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=> file biosis caba caplus lifesci medline
=> e jacobs jr william/au
E1          17     JACOBS JR W R/AU
E2           1     JACOBS JR W R JR/AU
E3           0 --> JACOBS JR WILLIAM/AU
E4           6     JACOBS JR WILLIAM R/AU
E5           3     JACOBS JR WILLIAM R JR/AU
E6           1     JACOBS JUCIA F/AU
E7           1     JACOBS JUDE T/AU
E8           4     JACOBS JUDITH/AU
E9           1     JACOBS JUDITH A/AU
E10          1     JACOBS JUDITH H/AU
E11         72     JACOBS JUDITH M/AU
E12          2     JACOBS JUDITH R/AU

=> s e1-e5 and tuberculosis
L1          23 ("JACOBS JR W R"/AU OR "JACOBS JR W R JR"/AU OR "JACOBS JR WILLI
               AM"/AU OR "JACOBS JR WILLIAM R"/AU OR "JACOBS JR WILLIAM R JR"/A
               U) AND TUBERCULOSIS
=> dup rem l1
PROCESSING COMPLETED FOR L1
L2           21 DUP REM L1 (2 DUPLICATES REMOVED)
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YOU HAVE REQUESTED DATA FROM 21 ANSWERS - CONTINUE? Y/(N):y

L2   ANSWER 1 OF 21  LIFESCI    COPYRIGHT 2008 CSA on STN
AN   2007:116413  LIFESCI <<LOGINID::20080330>>
TI   Two polyketide-synthase-associated acyltransferases are required for
     sulfolipid biosynthesis in Mycobacterium   ***tuberculosis***
AU   Bhatt, Kiranmai; Gurcha, Sudagar S.; Bhatt, Apoorva; Besra, Gurdyal S.;
       ***Jacobs Jr, William R.***
CS   Howard Hughes Medical Institute, Department of Microbiology and
     Immunology, Albert Einstein College of Medicine, 1300 Morris Park Avenue,
     Bronx, NY 10461, USA; E-mail: jacobsw@hhmi.org
SO   Microbiology, (20070200) vol. 153, no. 2, pp. 513-520.
     ISSN: 1350-0872.
DT   Journal
FS   J
LA   English
SL   English
AB   The methyl-branched fatty acyl components of sulfolipid-I (SL-I), a major
     glycolipid of the human pathogen Mycobacterium   ***tuberculosis***  , are
     synthesized by the polyketide synthase Pks2. Rv3824c (papA1), located
     downstream of pks2, encodes a protein that belongs to a subfamily of
     acyltransferases associated with mycobacterial polyketide synthases
     [polyketide synthase- associated proteins (PAPs)]. The presence of a
     conserved acyltransferase motif (HX sub(3)DX sub(14)Y) suggested a role
     for PapA1 in acylation of sulfated trehalose to form SL-I. Targeted
     deletion of the H37Rv papA1 resulted in loss of SL-I, demonstrating its
     role in mycobacterial sulfolipid biosynthesis. Furthermore, SL-I synthesis
     was restored in the mutant strain following complementation with papA1,
     but not with mutant alleles of papA1 containing alterations of key
     residues in the acyltransferase motif, confirming that PapA1 was an
     acyltransferase. While other M.   ***tuberculosis***   pks clusters are
     associated with a single PAP-encoding gene, it was demonstrated that
     another open reading frame, Rv3820c (papA2), located 5.8 kb downstream of
     papA1 is also an acyltransferase gene involved in SL-I biosynthesis:
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deletion of papA2 abolished SL-I production. The absence of any partially acylated intermediates in either null mutant indicated that both PapA1 and PapA2 were required for all acylation steps of SL-I assembly.

TI Two polyketide-synthase-associated acyltransferases are required for sulfolipid biosynthesis in Mycobacterium ***tuberculosis***

AU Bhatt, Kiranmai; Gurcha, Sudagar S.; Bhatt, Apoorva; Besra, Gurdyal S.; ***Jacobs Jr, William R.***

AB The methyl-branched fatty acyl components of sulfolipid-I (SL-I), a major glycolipid of the human pathogen Mycobacterium ***tuberculosis*** , are synthesized by the polyketide synthase Pks2. Rv3824c (papA1), located downstream of pks2, encodes a protein that belongs to a. . . of papA1 containing alterations of key residues in the acyltransferase motif, confirming that PapA1 was an acyltransferase. While other M. ***tuberculosis*** pks clusters are associated with a single PAP-encoding gene, it was demonstrated that another open reading frame, Rv3820c (papA2), located. . .

UT Acylation; Acyltransferase; Complementation; Gene deletion; Glycolipids; Open reading frames; Pathogens; Polyketide synthase; Trehalose; ***Tuberculosis*** ; polyketides; Mycobacterium ***tuberculosis***

L2 ANSWER 2 OF 21 LIFESCI COPYRIGHT 2008 CSA on STN

AN 2007:54295 LIFESCI <<LOGINID::20080330>>

TI Transfer of a point mutation in Mycobacterium ***tuberculosis*** inhA resolves the target of isoniazid

AU Vilcheze, Catherine; Wang, Feng; Arai, Masayoshi; Hazbon, Manzour Hernando; Colangeli, Roberto; Kremer, Laurent; Weisbrod, Torin R; Alland, David; Sacchettini, James C; ***Jacobs Jr, William R***

CS Howard Hughes Medical Institute, Department of Microbiology and Immunology, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, New York 10461, USA.; E-mail: jacobsw@hhmi.org

SO Nature Medicine [Nat. Med.], (20060900) vol. 12, no. 9, pp. 1027-1029. ISSN: 1078-8956.

DT Journal

FS G; J

LA English

SL English

AB Isoniazid is one of the most effective antituberculosis drugs, yet its precise mechanism of action is still controversial. Using specialized linkage transduction, a single point mutation allele (S94A) within the putative target gene inhA was transferred in Mycobacterium ***tuberculosis*** . The inhA(S94A) allele was sufficient to confer clinically relevant levels of resistance to isoniazid killing and inhibition of mycolic acid biosynthesis. This resistance correlated with the decreased binding of the INH-NAD inhibitor to InhA, as shown by enzymatic and X-ray crystallographic analyses, and establishes InhA as the primary target of isoniazid action in M. ***tuberculosis*** .

TI Transfer of a point mutation in Mycobacterium ***tuberculosis*** inhA resolves the target of isoniazid

AU. . . Catherine; Wang, Feng; Arai, Masayoshi; Hazbon, Manzour Hernando; Colangeli, Roberto; Kremer, Laurent; Weisbrod, Torin R; Alland, David; Sacchettini, James C; ***Jacobs Jr, William R***

AB . . . Using specialized linkage transduction, a single point mutation allele (S94A) within the putative target gene inhA was transferred in Mycobacterium ***tuberculosis*** . The inhA(S94A) allele was sufficient to confer clinically relevant levels of resistance to isoniazid killing and inhibition of mycolic acid. . . as shown by enzymatic and X-ray crystallographic analyses, and establishes InhA as the primary target of

isoniazid action in M. ***tuberculosis*** .
UT Isoniazid; Mycolic acids; Point mutation; Mycobacterium ***tuberculosis***

L2 ANSWER 3 OF 21 LIFESCI COPYRIGHT 2008 CSA on STN
AN 2003:114605 LIFESCI <<LOGINID::20080330>>
TI The primary mechanism of attenuation of bacillus Calmette-Guerin is a loss of secreted lytic function required for invasion of lung interstitial tissue
AU Hsu, T.; Hingley-Wilson, S.M.; Chen, B.; Chen, M.; Dai, A.Z.; Morin, P.M.; Marks, C.B.; Padiyar, J.; Goulding, C.; Gingery, M.; Eisenberg, D.; Russell, R.G.; Derrick, S.C.; Collins, F.M.; Morris, S.L.; King, C.H.; ***Jacobs Jr, W.R.***
CS Howard Hughes Medical Institute, Departments of Pathology and Microbiology and Immunology, and Analytic Imaging Facility, Albert Einstein College of Medicine, Bronx, NY 10461; E-mail: jacobsw@hhmi.org
SO Proceedings of the National Academy of Sciences, USA [Proc. Natl. Acad. Sci. USA], (20031014) vol. 100, no. 21, pp. 12420-12425. ISSN: 0027-8424.
DT Journal
FS G; J
LA English
SL English
AB ***Tuberculosis*** remains a leading cause of death worldwide, despite the availability of effective chemotherapy and a vaccine. Bacillus Calmette-Guerin (BCG), the ***tuberculosis*** vaccine, is an attenuated mutant of Mycobacterium bovis that was isolated after serial subcultures, yet the functional basis for this attenuation has never been elucidated. A single region (RD1), which is absent in all BCG substrains, was deleted from virulent M. bovis and Mycobacterium ***tuberculosis*** strains, and the resulting [Delta]RD1 mutants were significantly attenuated for virulence in both immunocompromised and immunocompetent mice. The M. ***tuberculosis*** [Delta]RD1 mutants were also shown to protect mice against aerosol challenge, in a similar manner to BCG. Interestingly, the [Delta]RD1 mutants failed to cause cytolysis of pneumocytes, a phenotype that had been previously used to distinguish virulent M. ***tuberculosis*** from BCG. A specific transposon mutation, which disrupts the Rv3874 Rv3875 (cfp-10 esat-6) operon of RD1, also caused loss of the cytolytic phenotype in both pneumocytes and macrophages. This mutation resulted in the attenuation of virulence in mice, as the result of reduced tissue invasiveness. Moreover, specific deletion of each transcriptional unit of RD1 revealed that three independent transcriptional units are required for virulence, two of which are involved in the secretion of ESAT-6 (6-kDa early secretory antigenic target). We conclude that the primary attenuating mechanism of bacillus Calmette-Guerin is the loss of cytolytic activity mediated by secreted ESAT-6, which results in reduced tissue invasiveness.
AU. . . Marks, C.B.; Padiyar, J.; Goulding, C.; Gingery, M.; Eisenberg, D.; Russell, R.G.; Derrick, S.C.; Collins, F.M.; Morris, S.L.; King, C.H.; ***Jacobs Jr, W.R.***
AB ***Tuberculosis*** remains a leading cause of death worldwide, despite the availability of effective chemotherapy and a vaccine. Bacillus Calmette-Guerin (BCG), the ***tuberculosis*** vaccine, is an attenuated mutant of Mycobacterium bovis that was isolated after serial subcultures, yet the functional basis for this. . . elucidated. A single region (RD1), which is absent in all BCG substrains, was deleted from virulent M. bovis and Mycobacterium ***tuberculosis*** strains,

and the resulting [Delta]RD1 mutants were significantly attenuated for virulence in both immunocompromised and immunocompetent mice. The M. ***tuberculosis*** [Delta]RD1 mutants were also shown to protect mice against aerosol challenge, in a similar manner to BCG. Interestingly, the [Delta]RD1 mutants failed to cause cytolysis of pneumocytes, a phenotype that had been previously used to distinguish virulent M. ***tuberculosis*** from BCG. A specific transposon mutation, which disrupts the Rv3874 Rv3875 (cfp-10 esat-6) operon of RD1, also caused loss of. . .

UT Lung diseases; ***Tuberculosis*** ; Gene regulation; RD1 gene; ESAT-6 protein; Mycobacterium ***tuberculosis*** ; Mycobacterium bovis; mice

L2 ANSWER 4 OF 21 LIFESCI COPYRIGHT 2008 CSA on STN DUPLICATE 1
AN 2003:91498 LIFESCI <<LOGINID::20080330>>
TI Vaccine Efficacy of a Lysine Auxotroph of Mycobacterium ***tuberculosis***
AU Pavelka, M.S.,Jr.; Chen, B.; Kelley, C.L.; Collins, F.M.; ***Jacobs Jr,*** *** W.R.****
CS Department of Microbiology and Immunology, Albert Einstein College of Medicine, 1300 Morris Park Ave., Bronx, NY 10461; E-mail: jacobs@aecom.yu.edu
SO Infection and Immunity [Infect. Immun.], (20030700) vol. 71, no. 7, pp. 4190-4192.
ISSN: 0019-9567.
DT Journal
FS F; J
LA English
SL English
AB The in vivo growth phenotype and vaccine efficacy of a lysine auxotrophic mutant of Mycobacterium ***tuberculosis*** strain H37Rv are described. An immunization experiment using a mouse model with an aerosol challenge showed that two doses of the M. ***tuberculosis*** mutant were required to generate protection equivalent to that of the Mycobacterium bovis BCG vaccine.
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AU Pavelka, M.S.,Jr.; Chen, B.; Kelley, C.L.; Collins, F.M.; ***Jacobs Jr,*** *** W.R.****
AB The in vivo growth phenotype and vaccine efficacy of a lysine auxotrophic mutant of Mycobacterium ***tuberculosis*** strain H37Rv are described. An immunization experiment using a mouse model with an aerosol challenge showed that two doses of the M. ***tuberculosis*** mutant were required to generate protection equivalent to that of the Mycobacterium bovis BCG vaccine.
UT ***Tuberculosis*** ; Vaccines; BCG; Aerosols; Mycobacterium ***tuberculosis*** ; Mycobacterium bovis; mice

L2 ANSWER 5 OF 21 LIFESCI COPYRIGHT 2008 CSA on STN
AN 2003:41745 LIFESCI <<LOGINID::20080330>>
TI Crystal structure of Mycobacterium ***tuberculosis*** SecA, a preprotein translocating ATPase
AU Sharma, V.; Arockiasamy, A.; Ronning, D.R.; Savva, C.G.; Holzenburg, A.; Braunstein, M.; ***Jacobs Jr, W.R.*** ; Sacchettini, J.C.
CS Center for Structural Biology, Institute of Biosciences and Technology, Houston, TX 77030; E-mail: sacchett@tamu.edu

SO Proceedings of the National Academy of Sciences, USA [Proc. Natl. Acad. Sci. USA], (20030304) vol. 100, no. 5, pp. 2243-2248.
ISSN: 0027-8424.
DT Journal
FS J
LA English
SL English
AB In bacteria, the majority of exported proteins are translocated by the Sec system, which recognizes the signal sequence of a preprotein and uses ATP and the proton motive force to mediate protein translocation across the cytoplasmic membrane. SecA is an essential protein component of this system, containing the molecular motor that facilitates translocation. Here we report the three-dimensional structure of the SecA protein of Mycobacterium ***tuberculosis*** . Each subunit of the homodimer contains a "motor" domain and a translocation domain. The structure predicts that SecA can interact with the SecYEG pore and function as a molecular ratchet that uses ATP hydrolysis for physical movement of the preprotein. Knowledge of this structure provides a framework for further elucidation of the translocation process.
TI Crystal structure of Mycobacterium ***tuberculosis*** SecA, a preprotein translocating ATPase
AU Sharma, V.; Arockiasamy, A.; Ronning, D.R.; Savva, C.G.; Holzenburg, A.; Braunstein, M.; ***Jacobs Jr, W.R.*** ; Sacchettini, J.C.
AB . . . system, containing the molecular motor that facilitates translocation. Here we report the three-dimensional structure of the SecA protein of Mycobacterium ***tuberculosis*** . Each subunit of the homodimer contains a "motor" domain and a translocation domain. The structure predicts that SecA can interact. . .
UT Crystal structure; Adenosinetriphosphatase; Protein export; SecA protein; Mycobacterium ***tuberculosis***

L2 ANSWER 6 OF 21 LIFESCI COPYRIGHT 2008 CSA on STN
AN 2002:49487 LIFESCI <<LOGINID::20080330>>
TI Crystal Structures of Mycolic Acid Cyclopropane Synthases from Mycobacterium ***tuberculosis***
AU Huang, C.; Smith, C.V.; Glickman, M.S.; ***Jacobs Jr., W.R.*** ; Sacchettini, J.C.
CS Department of Biochemistry, Texas A&M University, College Station, Texas 77843-2128, USA; E-mail: sacchett@tamu.edu
SO Journal of Biological Chemistry [J. Biol. Chem.], (20020329) vol. 277, no. 13, pp. 11559-11569.
ISSN: 0021-9258.
DT Journal
FS J
LA English
SL English
AB Mycolic acids are major components of the cell wall of Mycobacterium ***tuberculosis*** . Several studies indicate that functional groups in the acyl chain of mycolic acids are important for pathogenesis and persistence. There are at least three mycolic acid cyclopropane synthases (PcaA, CmaA1, and CmaA2) that are responsible for these site-specific modifications of mycolic acids. To derive information on the specificity and enzyme mechanism of the family of proteins, the crystal structures of CmaA1, CmaA2, and PcaA were solved to 2-, 2-, and 2.65-Aa resolution, respectively. All three enzymes have a seven-stranded alpha / beta fold similar to other methyltransferases with the location and interactions with the cofactor S-adenosyl-L-methionine conserved. The structures of the

ternary complexes demonstrate the position of the mycolic acid substrate binding site. Close examination of the active site reveals electron density that we believe represents a bicarbonate ion. The structures support the hypothesis that these enzymes catalyze methyl transfer via a carbocation mechanism in which the bicarbonate ion acts as a general base. In addition, comparison of the enzyme structures reveals a possible mechanism for substrate specificity. These structures provide a foundation for rational-drug design, which may lead to the development of new inhibitors effective against persistent bacteria.

TI Crystal Structures of Mycolic Acid Cyclopropane Synthases from Mycobacterium ***tuberculosis***

AU Huang, C.; Smith, C.V.; Glickman, M.S.; ***Jacobs Jr., W.R.*** ; Sacchettini, J.C.

AB Mycolic acids are major components of the cell wall of Mycobacterium ***tuberculosis*** . Several studies indicate that functional groups in the acyl chain of mycolic acids are important for pathogenesis and persistence. There. . .

UT Crystal structure; Pathogenesis; Substrate specificity; PcaA protein; CmaA1 protein; CmaA2 protein; mycolic acid cyclopropane synthases; Mycobacterium ***tuberculosis***

L2 ANSWER 7 OF 21 LIFESCI COPYRIGHT 2008 CSA on STN DUPLICATE 2

AN 2002:117827 LIFESCI <<LOGINID::20080330>>

TI Whole-Genome Comparison of Mycobacterium ***tuberculosis*** Clinical and Laboratory Strains

AU Fleischmann, R.D.*; Alland, D.; Eisen, J.A.; Carpenter, L.; White, O.; Peterson, J.; DeBoy, R.; Dodson, R.; Gwinn, M.; Haft, D.; Hickey, E.; Kolonay, J.F.; Nelson, W.C.; Umayam, L.A.; Ermolaeva, M.; Salzberg, S.L.; Delcher, A.; Utterback, T.; Weidman, J.; Khouri, H.; Gill, J.; Mikula, A.; Bishai, W.; ***Jacobs Jr., W.R.*** ; Venter, J.C.; Fraser, C.M.

CS The Institute for Genomic Research, 9712 Medical Center Dr., Rockville, MD 20850; E-mail: rdfleisc@tigr.org

SO Journal of Bacteriology [J. Bacteriol.], (20021000) vol. 184, no. 19, pp. 5479-5490.
ISSN: 0021-9193.

DT Journal

FS J

LA English

SL English

AB Virulence and immunity are poorly understood in Mycobacterium ***tuberculosis*** . We sequenced the complete genome of the M. ***tuberculosis*** clinical strain CDC1551 and performed a whole-genome comparison with the laboratory strain H37Rv in order to identify polymorphic sequences with potential relevance to disease pathogenesis, immunity, and evolution. We found large-sequence and single-nucleotide polymorphisms in numerous genes. Polymorphic loci included a phospholipase C, a membrane lipoprotein, members of an adenylate cyclase gene family, and members of the PE/PPE gene family, some of which have been implicated in virulence or the host immune response. Several gene families, including the PE/PPE gene family, also had significantly higher synonymous and nonsynonymous substitution frequencies compared to the genome as a whole. We tested a large sample of M. ***tuberculosis*** clinical isolates for a subset of the large-sequence and single-nucleotide polymorphisms and found widespread genetic variability at many of these loci. We performed phylogenetic and epidemiological analysis to investigate the evolutionary relationships among isolates and the origins of specific polymorphic loci. A number of these polymorphisms appear to have occurred multiple times as

independent events, suggesting that these changes may be under selective pressure. Together, these results demonstrate that polymorphisms among M. ***tuberculosis*** strains are more extensive than initially anticipated, and genetic variation may have an important role in disease pathogenesis and immunity.

TI Whole-Genome Comparison of Mycobacterium ***tuberculosis*** Clinical and Laboratory Strains

AU. . . Umayam, L.A.; Ermolaeva, M.; Salzberg, S.L.; Delcher, A.; Utterback, T.; Weidman, J.; Khouri, H.; Gill, J.; Mikula, A.; Bishai, W.; ***Jacobs*** *** Jr., W.R.*** ; Venter, J.C.; Fraser, C.M.

AB Virulence and immunity are poorly understood in Mycobacterium ***tuberculosis*** . We sequenced the complete genome of the M. ***tuberculosis*** clinical strain CDC1551 and performed a whole-genome comparison with the laboratory strain H37Rv in order to identify polymorphic sequences with. . . higher synonymous and nonsynonymous substitution frequencies compared to the genome as a whole. We tested a large sample of M. ***tuberculosis*** clinical isolates for a subset of the large-sequence and single-nucleotide polymorphisms and found widespread genetic variability at many of these. . . as independent events, suggesting that these changes may be under selective pressure. Together, these results demonstrate that polymorphisms among M. ***tuberculosis*** strains are more extensive than initially anticipated, and genetic variation may have an important role in disease pathogenesis and immunity.

UT Genetic diversity; Epidemiology; Phylogeny; Pathogenesis; Immunity; Selection; Single-nucleotide polymorphism; Phospholipase C; Nucleotide sequence; ***Tuberculosis*** ; Gene polymorphism; Mycobacterium ***tuberculosis***

L2 ANSWER 8 OF 21 LIFESCI COPYRIGHT 2008 CSA on STN

AN 2003:2799 LIFESCI <<LOGINID::20080330>>

TI Infection of Mice with Aerosolized Mycobacterium ***tuberculosis*** : Use of a Nose-Only Apparatus for Delivery of Low Doses of Inocula and Design of an Ultrasafe Facility

AU Schwebach, J.R.; Chen, B.; Glatman-Freedman, A.; Casadevall, A.; McKinney, J.D.; Harb, J.L.; McGuire, P.J.; Barkley, W.E.; Bloom, B.R.; ***Jacobs,*** *** JR., W.R.****

CS Albert Einstein College of Medicine, 1300 Morris Park Ave., Bronx, NY 10461; E-mail: jacobs@accom.yu.edu

SO Applied and Environmental Microbiology [Appl. Environ. Microbiol.], (20020900) vol. 68, no. 9, pp. 4646-4649.
ISSN: 0099-2240.

DT Journal

FS A

LA English

SL English

AB Aerosolized delivery of virulent or hypervirulent Mycobacterium ***tuberculosis*** requires careful consideration of methodology and safety. To maximize safety, we installed a nose-only aerosol apparatus that can reproducibly deliver a low dose (<100 CFU per mouse) of M. ***tuberculosis*** in a carefully designed biohazard facility.

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AU Schwebach, J.R.; Chen, B.; Glatman-Freedman, A.; Casadevall, A.; McKinney,

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UT ***Tuberculosis*** ; Inoculation route; Aerosols; Animal models; Dose; Mycobacterium ***tuberculosis*** ; mice

L2 ANSWER 9 OF 21 LIFESCI COPYRIGHT 2008 CSA on STN

AN 2002:46684 LIFESCI <<LOGINID::20080330>>

TI Mycobacterium ***tuberculosis*** WhiB3 interacts with RpoV to affect host survival but is dispensable for in vivo growth

AU Steyn, A.J.C.; Collins, D.M.; Hondalus, M.K.; ***Jacobs Jr., W.R.*** ; Kawakami, R.P.; Bloom, B.R.

CS Harvard School of Public Health, Department of Immunology and Infectious Disease, Boston, MA 02115, USA; E-mail: bbloom@hsph.harvard.edu

SO Proceedings of the National Academy of Sciences, USA [Proc. Natl. Acad. Sci. USA], (20020305) vol. 99, no. 5, pp. 3147-3152. ISSN: 0027-8424.

DT Journal

FS G; J

LA English

SL English

AB Previous work established that the principal sigma factor (RpoV) of virulent Mycobacterium bovis, a member of the Mycobacterium ***tuberculosis*** complex, restores virulence to an attenuated strain containing a point mutation (Arg-515 arrow right His) in the 4.2 domain of RpoV. We used the 4.2 domain of RpoV as bait in a yeast two-hybrid screen of an M. ***tuberculosis*** H37Rv library and identified a putative transcription factor, WhiB3, which selectively interacts with the 4.2 domain of RpoV in virulent strains but not with the mutated (Arg-515 arrow right His) allele. Infection of mice and guinea pigs with a M. ***tuberculosis*** H37Rv whiB3 deletion mutant strain showed that whiB3 is not necessary for in vivo bacterial replication in either animal model. In contrast, an M. bovis whiB3 deletion mutant was completely attenuated for growth in guinea pigs. However, we found that immunocompetent mice infected with the M. ***tuberculosis*** H37Rv whiB3 mutant strain had significantly longer mean survival times as compared with mice challenged with wild-type M. ***tuberculosis*** . Remarkably, the bacterial organ burdens of both mutant and wild-type infected mice were identical during the acute and persistent phases of infection. Our results imply that M. ***tuberculosis*** replication per se is not a sufficient condition for virulence in vivo. They also indicate a different role for M. bovis and M. ***tuberculosis*** whiB3 genes in pathogenesis generated in different animal models. We propose that M. ***tuberculosis*** WhiB3 functions as a transcription factor regulating genes that influence the immune response of the host.

TI Mycobacterium ***tuberculosis*** WhiB3 interacts with RpoV to affect host survival but is dispensable for in vivo growth

AU Steyn, A.J.C.; Collins, D.M.; Hondalus, M.K.; ***Jacobs Jr., W.R.*** ; Kawakami, R.P.; Bloom, B.R.

AB Previous work established that the principal sigma factor (RpoV) of virulent Mycobacterium bovis, a member of the Mycobacterium ***tuberculosis*** complex, restores virulence to an attenuated strain

containing a point mutation (Arg-515 arrow right His) in the 4.2 domain of RpoV. We used the 4.2 domain of RpoV as bait in a yeast two-hybrid screen of an M. ***tuberculosis*** H37Rv library and identified a putative transcription factor, WhiB3, which selectively interacts with the 4.2 domain of RpoV in virulent. . . strains but not with the mutated (Arg-515 arrow right His) allele. Infection of mice and guinea pigs with a M. ***tuberculosis*** H37Rv whiB3 deletion mutant strain showed that whiB3 is not necessary for in vivo bacterial replication in either animal model.. . . deletion mutant was completely attenuated for growth in guinea pigs. However, we found that immunocompetent mice infected with the M. ***tuberculosis*** H37Rv whiB3 mutant strain had significantly longer mean survival times as compared with mice challenged with wild-type M. ***tuberculosis*** . Remarkably, the bacterial organ burdens of both mutant and wild-type infected mice were identical during the acute and persistent phases of infection. Our results imply that M. ***tuberculosis*** replication per se is not a sufficient condition for virulence in vivo. They also indicate a different role for M. bovis and M. ***tuberculosis*** whiB3 genes in pathogenesis generated in different animal models. We propose that M. ***tuberculosis*** WhiB3 functions as a transcription factor regulating genes that influence the immune response of the host.

UT Replication; Deletion mutant; Immune response; Virulence; Transcription factors; Gene regulation; ***Tuberculosis*** ; RpoV protein; WhiB3 protein; Mycobacterium ***tuberculosis*** ; mice; guinea-pigs

L2 ANSWER 10 OF 21 MEDLINE on STN
AN 2002640998 MEDLINE <<LOGINID::20080330>>
DN PubMed ID: 12368434
TI Specialized transduction: an efficient method for generating marked and unmarked targeted gene disruptions in Mycobacterium ***tuberculosis*** , M. bovis BCG and M. smegmatis.
AU Bardarov Stoyan; Bardarov Jr Svetoslav Jr; Pavelka Jr Martin S Jr; Sambandamurthy Vasan; Larsen Michelle; Tufariello JoAnn; Chan John; Hatfull Graham; ***Jacobs Jr William R Jr***
CS Dept of Microbiology and Immunology and Howard Hughes Medical Institute, Albert Einstein College of Medicine, Bronx, NY 10461, USA.
NC AI26170 (United States NIAID)
AI28927 (United States NIAID)
AI46690 (United States NIAID)
AI49375 (United States NIAID)
GMG2410 (United States NIGMS)
SO Microbiology (Reading, England), (2002 Oct) Vol. 148, No. Pt 10, pp. 3007-17.
Journal code: 9430468. ISSN: 1350-0872.
CY England: United Kingdom
DT (EVALUATION STUDIES)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LA English
FS Priority Journals
EM 200301
ED Entered STN: 29 Oct 2002
Last Updated on STN: 11 Jan 2003
Entered Medline: 10 Jan 2003
AB The authors have developed a simple and highly efficient system for generating allelic exchanges in both fast- and slow-growing mycobacteria. In this procedure a gene of interest, disrupted by a selectable marker, is

cloned into a conditionally replicating (temperature-sensitive) shuttle phasmid to generate a specialized transducing mycobacteriophage. The temperature-sensitive mutations in the mycobacteriophage genome permit replication at the permissive temperature of 30 degrees C but prevent replication at the non-permissive temperature of 37 degrees C. Transduction at a non-permissive temperature results in highly efficient delivery of the recombination substrate to virtually all cells in the recipient population. The deletion mutations in the targeted genes are marked with antibiotic-resistance genes that are flanked by gammadelta-res (resolvase recognition target) sites. The transductants which have undergone a homologous recombination event can be conveniently selected on antibiotic-containing media. To demonstrate the utility of this genetic system seven different targeted gene disruptions were generated in three substrains of Mycobacterium bovis BCG, three strains of Mycobacterium ***tuberculosis*** , and Mycobacterium smegmatis. Mutants in the lysA, nadBC, panC, panCD, leuCD, Rv3291c and Rv0867c genes or operons were isolated as antibiotic-resistant (and in some cases auxotrophic) transductants. Using a plasmid encoding the gammadelta-resolvase (tnpR), the resistance genes could be removed, generating unmarked deletion mutations. It is concluded from the high frequency of allelic exchange events observed in this study that specialized transduction is a very efficient technique for genetic manipulation of mycobacteria and is a method of choice for constructing isogenic strains of M. ***tuberculosis*** , BCG or M. smegmatis which differ by defined mutations.

TI Specialized transduction: an efficient method for generating marked and unmarked targeted gene disruptions in Mycobacterium ***tuberculosis*** , M. bovis BCG and M. smegmatis.

AU. . . Stoyan; Bardarov Jr Svetoslav Jr; Pavelka Jr Martin S Jr; Sambandamurthy Vasan; Larsen Michelle; Tufariello JoAnn; Chan John; Hatfull Graham; ***Jacobs Jr William R Jr***

AB . . . genetic system seven different targeted gene disruptions were generated in three substrains of Mycobacterium bovis BCG, three strains of Mycobacterium ***tuberculosis*** , and Mycobacterium smegmatis. Mutants in the lysA, nadBC, panC, panCD, leuCD, Rv3291c and Rv0867c genes or operons were isolated as. . . very efficient technique for genetic manipulation of mycobacteria and is a method of choice for constructing isogenic strains of M. ***tuberculosis*** , BCG or M. smegmatis which differ by defined mutations.

CT . . . GE, genetics
*Gene Deletion
Genetic Markers
*Mycobacteriophages: GE, genetics
*Mycobacterium: GE, genetics
Mycobacterium bovis: GE, genetics
Mycobacterium smegmatis: GE, genetics
*** Mycobacterium tuberculosis: GE, genetics***
Plasmids
*Recombination, Genetic
*Transduction, Genetic: MT, methods

L2 ANSWER 11 OF 21 MEDLINE on STN
AN 2002611620 MEDLINE <<LOGINID::20080330>>
DN PubMed ID: 12368431
TI Characterization of a Mycobacterium ***tuberculosis*** H37Rv transposon library reveals insertions in 351 ORFs and mutants with altered virulence.

AU McAdam Ruth A; Quan Selwyn; Smith Debbie A; Bardarov Stoyan; Betts Joanna C; Cook Fiona C; Hooker Elizabeth U; Lewis Alan P; Woollard Peter; Everett Martin J; Lukey Pauline T; Bancroft Gregory J; ***Jacobs Jr William R*** *** Jr*** ; Duncan Ken

CS GlaxoSmithKline, Medicines Research Centre, Gunnels Wood Road, Stevenage SG1 2NY, UK.

SO Microbiology (Reading, England), (2002 Oct) Vol. 148, No. Pt 10, pp. 2975-86.
Journal code: 9430468. ISSN: 1350-0872.

CY England: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 200301

ED Entered STN: 8 Oct 2002
Last Updated on STN: 11 Jan 2003
Entered Medline: 10 Jan 2003

AB A library of Mycobacterium ***tuberculosis*** insertional mutants was generated with the transposon Tn5370. The junction sequence between the transposon and the mycobacterial chromosome was determined, revealing the positions of 1329 unique insertions, 1189 of which were located in 351 different ORFs. Transposition was not completely random and examination of the most susceptible genome regions revealed a lower-than-average G+C content ranging from 54 to 62 mol%. Mutants were obtained in all of the recognized M. ***tuberculosis*** functional protein-coding gene classes. About 30% of the disrupted ORFs had matches elsewhere in the genome that suggested redundancy of function. The effect of gene disruption on the virulence of a selected set of defined mutants was investigated in a severe combined immune deficiency (SCID) mouse model. A range of phenotypes was observed in these mutants, the most notable being the severe attenuation in virulence of a strain disrupted in the Rv1290c gene, which encodes a protein of unknown function. The library described in this study provides a resource of defined mutant strains for use in functional analyses aimed at investigating the role of particular M. ***tuberculosis*** genes in virulence and defining their potential as targets for new anti-mycobacterial drugs or as candidates for deletion in a rationally attenuated live vaccine.

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CT Animals
*DNA Transposable Elements: GE, genetics

Disease Models, Animal
*Gene Library
Humans
Mice
Mice, SCID
*Mutagenesis, Insertional
Mutation
*** Mycobacterium tuberculosis: GE, genetics***
****Mycobacterium tuberculosis: PY, pathogenicity***
Open Reading Frames: GE, genetics
****Tuberculosis, Pulmonary: MI, microbiology***
Virulence

L2 ANSWER 12 OF 21 LIFESCI COPYRIGHT 2008 CSA on STN
AN 2002:24936 LIFESCI <<LOGINID::20080330>>
TI Evidence that Mycobacterial PE_PGRS Proteins Are Cell Surface Constituents That Influence Interactions with Other Cells
AU Brennan, M.J.*; Delogu, G.; Chen, Y.; Bardarov, S.; Kriakov, J.; Alavi, M.; ***Jacobs Jr., W.R.***
CS CBER/FDA, Building 29, Room 502, 29 Lincoln Dr. (HFM-431), Bethesda, MD 20892.; E-mail: Brennan@cber.fda.gov
SO Infection and Immunity [Infect. Immun.], (20011200) vol. 69, no. 12, pp. 7326-7333.
ISSN: 0019-9567.
DT Journal
FS J; G
LA English
SL English
AB The elucidation of the genomic sequence of Mycobacterium ***tuberculosis*** revealed the presence of a novel multigene family designated PE/PE_PGRS that encodes numerous, highly related proteins of unknown function. In this study, we demonstrate that a transposon insertion in a PE_PGRS gene (1818 super(PE_PGRS)) found in Mycobacterium bovis BCG Pasteur, which is the BCG homologue of the M. ***tuberculosis*** H37Rv gene Rv1818c, introduces new phenotypic properties to this BCG strain. These properties include dispersed growth in liquid medium and reduced infection of macrophages. Complementation of the 1818 super(PE_PGRS)::Tn5367 mutant with the wild-type gene restores both aggregative growth (clumping) in liquid medium and reestablishes infectivity of macrophages to levels equivalent to those for the parent BCG strain. Western blot analysis using antisera raised against the 1818 super(PE_PGRS) protein shows that PE_PGRS proteins are found in cell lysates of BCG and M. ***tuberculosis*** H37Ra and in the cell wall fraction of M. ***tuberculosis*** H37Rv. Moreover, immunofluorescent labeling of mycobacteria indicates that certain PE_PGRS proteins are localized at the cell surface of BCG and M. ***tuberculosis*** . Together these results suggest that certain PE_PGRS proteins may be found at the surface of mycobacteria and influence both cell surface interactions among mycobacteria as well as the interactions of mycobacteria with macrophages.
AU Brennan, M.J.*; Delogu, G.; Chen, Y.; Bardarov, S.; Kriakov, J.; Alavi, M.; ***Jacobs Jr., W.R.***
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tuberculosis H37Rv gene Rv1818c, introduces new phenotypic properties to this BCG strain. These properties include dispersed growth in liquid medium and. . . antisera raised against the 1818 super(PE_PGRS) protein shows that PE_PGRS proteins are found in cell lysates of BCG and M. ***tuberculosis*** H37Ra and in the cell wall fraction of M. ***tuberculosis*** H37Rv. Moreover, immunofluorescent labeling of mycobacteria indicates that certain PE_PGRS proteins are localized at the cell surface of BCG and M. ***tuberculosis*** . Together these results suggest that certain PE_PGRS proteins may be found at the surface of mycobacteria and influence both cell. . .

L2 ANSWER 13 OF 21 LIFESCI COPYRIGHT 2008 CSA on STN
AN 2001:111304 LIFESCI <<LOGINID::20080330>>
TI The Alternative Sigma Factor SigH Regulates Major Components of Oxidative and Heat Stress Responses in Mycobacterium ***tuberculosis***
AU Raman, S.; Song, T.; Puyang, X.; Bardarov, S.; ***Jacobs Jr., W.R.*** ; Husson, R.N.*
CS Children's Hospital, Enders Rm. 609, 300 Longwood Ave., Boston, MA 02115.; E-mail: robert.husson@tch.harvard.edu
SO Journal of Bacteriology [J. Bacteriol.], (20011000) vol. 183, no. 20, pp. 6119-6125.
ISSN: 0021-9193.
DT Journal
FS G; J
LA English
SL English
AB Mycobacterium ***tuberculosis*** is a specialized intracellular pathogen that must regulate gene expression to overcome stresses produced by host defenses during infection. SigH is an alternative sigma factor that we have previously shown plays a role in the response to stress of the saprophyte Mycobacterium smegmatis. In this work we investigated the role of sigH in the M. ***tuberculosis*** response to heat and oxidative stress. We determined that a M. ***tuberculosis*** sigH mutant is more susceptible to oxidative stresses and that the inducible expression of the thioredoxin reductase/thioredoxin genes trxB2/trxC and a gene of unknown function, Rv2466c, is regulated by sigH via expression from promoters directly recognized by SigH. We also determined that the sigH mutant is more susceptible to heat stress and that inducible expression of the heat shock genes dnaK and clpB is positively regulated by sigH. The induction of these heat shock gene promoters but not of other SigH-dependent promoters was markedly greater in response to heat versus oxidative stress, consistent with their additional regulation by a heat-labile repressor. To further understand the role of sigH in the M. ***tuberculosis*** stress response, we investigated the regulation of the stress-responsive sigma factor genes sigE and sigB. We determined that inducible expression of sigE is regulated by sigH and that basal and inducible expression of sigB is dependent on sigE and sigH. These data indicate that sigH plays a central role in a network that regulates heat and oxidative-stress responses that are likely to be important in M. ***tuberculosis*** pathogenesis.
TI The Alternative Sigma Factor SigH Regulates Major Components of Oxidative and Heat Stress Responses in Mycobacterium ***tuberculosis***
AU Raman, S.; Song, T.; Puyang, X.; Bardarov, S.; ***Jacobs Jr., W.R.*** ; Husson, R.N.*
AB Mycobacterium ***tuberculosis*** is a specialized intracellular pathogen that must regulate gene expression to overcome stresses produced by host defenses during infection. SigH. . . response to stress of the

saprophyte Mycobacterium smegmatis. In this work we investigated the role of sigH in the M. ***tuberculosis*** response to heat and oxidative stress. We determined that a M. ***tuberculosis*** sigH mutant is more susceptible to oxidative stresses and that the inducible expression of the thioredoxin reductase/thioredoxin genes trxB2/trxC and. . . stress, consistent with their additional regulation by a heat-labile repressor. To further understand the role of sigH in the M. ***tuberculosis*** stress response, we investigated the regulation of the stress-responsive sigma factor genes sigE and sigB. We determined that inducible expression. . . a central role in a network that regulates heat and oxidative-stress responses that are likely to be important in M. ***tuberculosis*** pathogenesis.

UT ***Tuberculosis*** ; Oxidative stress; Temperature effects; Sigma factor; Heat shock; SigH protein; sigH gene; dnaK gene; clpB gene; Mycobacterium ***tuberculosis***

L2 ANSWER 14 OF 21 LIFESCI COPYRIGHT 2008 CSA on STN

AN 2001:115454 LIFESCI <<LOGINID::20080330>>

TI Luciferase Reporter Mycobacteriophages for Detection, Identification, and Antibiotic Susceptibility Testing of Mycobacterium ***tuberculosis*** in Mexico

AU Banaiee, N.*; Bobadilla-del-Valle, M.; Bardarov Jr., S.; Riska, P.F.; Small, P.M.; Ponce-de-Leon, A.; ***Jacobs Jr., W.R.*** ; Hatfull, G.F.; Sifuentes-Osornio, J.

CS Department of Laboratory Medicine, UCSF, L518 Box 0134, San Francisco, CA 94143-0134.; E-mail: niaz@itsa.ucsf.edu

SO Journal of Clinical Microbiology [J. Clin. Microbiol.], (20011100) vol. 39, no. 11, pp. 3883-3888.
ISSN: 0095-1137.

DT Journal

FS J; A

LA English

SL English

AB The utility of luciferase reporter mycobacteriophages (LRPs) for detection, identification, and antibiotic susceptibility testing of Mycobacterium ***tuberculosis*** was prospectively evaluated in a clinical microbiology laboratory in Mexico City, Mexico. Five hundred twenty-three consecutive sputum samples submitted to the laboratory during a 5-month period were included in this study. These specimens were cultivated in Middlebrook 7H9 (MADC), MGIT, and Loewenstein-Jensen (LJ) media. Of the 71 mycobacterial isolates recovered with any of the three media, 76% were detected with the LRPs, 97% were detected with the MGIT 960 method, and 90% were detected with LJ medium. When contaminated specimens were excluded from the analysis, the LRPs detected 92% (54 of 59) of the cultures. The median time to detection of bacteria was 7 days with both the LRPs and the MGIT 960 method. LRP detection of growth in the presence of p-nitro- alpha -acetylamino- beta -hydroxypropiophenone (NAP) was used for selective identification of M. ***tuberculosis*** complex (MTC) and compared to identification with BACTEC 460. Using the LRP NAP test, 47 (94%) out of 50 isolates were correctly identified as ***tuberculosis*** complex. The accuracy and speed of LRP antibiotic susceptibility testing with rifampin, streptomycin, isoniazid, and ethambutol were compared to those of the BACTEC 460 method, and discrepant results were checked by the conventional proportion method. In total, 50 MTC isolates were tested. The overall agreement between the LRP and BACTEC 460 results was 98.5%. The median LRP-based susceptibility turnaround time was 2 days (range, 2 to 4 days) compared to 10.5 days (range, 7 to 16

days) by the BACTEC 460 method. Phage resistance was not detected in any of the 243 MTC isolates tested. Mycobacteriophage-based approaches to ***tuberculosis*** diagnostics can be implemented in clinical laboratories with sensitivity, specificity, and rapidity that compare favorably with those of the MGIT 960 and BACTEC 460 methods. The phages currently provide the fastest phenotypic assay for susceptibility testing.

TI Luciferase Reporter Mycobacteriophages for Detection, Identification, and Antibiotic Susceptibility Testing of Mycobacterium ***tuberculosis*** in Mexico

AU Banaiee, N.*; Bobadilla-del-Valle, M.; Bardarov Jr., S.; Riska, P.F.; Small, P.M.; Ponce-de-Leon, A.; ***Jacobs Jr., W.R.*** ; Hatfull, G.F.; Sifuentes-Osornio, J.

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UT Antitubercular agents; Antimycobacterial agents; Antibiotic sensitivity testing; Sputum; Diagnostic agents; Media (isolation); Drug sensitivity testing; Bactec test; ***Tuberculosis*** ; Phages; luciferase; Mexico; Mycobacterium ***tuberculosis*** ; mycobacteriophages

L2 ANSWER 15 OF 21 LIFESCI COPYRIGHT 2008 CSA on STN

AN 2001:19227 LIFESCI <<LOGINID::20080330>>

TI The Mycobacterium ***tuberculosis*** cmaA2 Gene Encodes a Mycolic Acid trans-Cyclopropane Synthetase

AU Glickman, M.S.; Cahill, S.M.; ***Jacobs Jr., W.R.***

CS Division of Infectious Diseases, Montefiore Medical Center, Albert Einstein College of Medicine; E-mail: glickman@aecom.yu.edu

SO Journal of Biological Chemistry [J. Biol. Chem.], (20010119) vol. 276, no. 3, pp. 2228-2233.
ISSN: 0021-9258.

DT Journal

FS G; J

LA English

SL English

AB Infection with Mycobacterium ***tuberculosis*** remains a major global health emergency. Although detailed understanding of the molecular events of M. ***tuberculosis*** pathogenesis is still limited, recent genetic analyses have implicated specific lipids of the cell envelope as important effectors in M. ***tuberculosis*** pathogenesis. We have shown that pcaA, a novel member of a family of M. ***tuberculosis*** S-adenosyl methionine (SAM)-dependent methyl transferases, is required for alpha -mycolic acid cyclopropanation and lethal chronic persistent M.

tuberculosis infection. To examine the apparent redundancy between
pcaA and cmaA2, another cyclopropane synthetase of M. ***tuberculosis*** thought to be involved in alpha -mycolate synthesis, we have disrupted the cmaA2 gene in virulent M. ***tuberculosis*** by specialized transduction. Inactivation of cmaA2 causes accumulation of unsaturated derivatives of both the methoxy- and ketomycolates. Analysis by proton NMR indicates that the mycolic acids of the cmaA2 mutant lack trans-cyclopropane rings but are otherwise intact with respect to cyclopropane and methyl branch content. Thus, cmaA2 is required for the synthesis of the trans cyclopropane rings of both the methoxymycolates and ketomycolates. These results define cmaA2 as a trans-cyclopropane synthetase and expand our knowledge of the substrate specificity of a large family of highly homologous mycolic acid methyl transferases recently shown to be critical to M. ***tuberculosis*** pathogenesis.

TI The Mycobacterium ***tuberculosis*** cmaA2 Gene Encodes a Mycolic Acid trans-Cyclopropane Synthetase

AU Glickman, M.S.; Cahill, S.M.; ***Jacobs Jr., W.R.***

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UT ***Tuberculosis*** ; Envelopes; cyclopropane synthase; pcaA gene; alpha -mycolic acid; cmaA2 gene; mycolic acid methyl transferase; Mycobacterium ***tuberculosis***

L2 ANSWER 16 OF 21 LIFESCI COPYRIGHT 2008 CSA on STN

AN 2002:49122 LIFESCI <<LOGINID::20080330>>

TI DIM mutants of mycobacteria and use thereof

AU Cox, J.S.; ***Jacobs, Jr., W.R.***

CS Albert Einstein College of Medicine of Yeshiva University

SO (20010918) . US Patent: 6290966; US CLASS: 424/200.1; 424/248.1; 435/7.4; 435/7.6; 435/7.91; 435/69.1; 435/183; 435/252.3; 435/253.1.

DT Patent

FS W3

LA English

SL English

AB Disclosed are novel recombinant mutant strains of mycobacteria that are deficient for the synthesis or transport of dimycoserosalphthiocerol ("DIM"). The present invention also provides a method of producing a recombinant mutant mycobacterium that is deficient for the synthesis or transport of DIM, comprising mutating a nucleic acid responsible for the synthesis or transport of dimycoserosalphthiocerol, including a nucleic

acid comprising the promoter for the pps operon, fadD28 or mmpL7. The present invention also provides a vaccine comprising a DIM mutant mycobacterium of the present invention, as well as a method for the treatment or prevention of ***tuberculosis*** in a subject using the vaccine.

AU Cox, J.S.; ***Jacobs, Jr., W.R.***

AB . . . comprising a DIM mutant mycobacterium of the present invention, as well as a method for the treatment or prevention of ***tuberculosis*** in a subject using the vaccine.

UT Patents; Promoters; Vaccines; ***Tuberculosis*** ; dimycoserosalphthiocerol; Mycobacterium

L2 ANSWER 17 OF 21 LIFESCI COPYRIGHT 2008 CSA on STN

AN 2002:49129 LIFESCI <<LOGINID::20080330>>

TI Mycobacterial species-specific reporter mycobacteriophages

AU ***Jacobs, Jr., W.R.*** ; Bloom, B.R.; Hatfull, G.F.

CS Albert Einstein College of Medicine of Yeshiva University

SO (20011009) . US Patent: 6300061; US CLASS: 435/6.

DT Patent

FS W3

LA English

SL English

AB This invention relates to mycobacterial species-specific reporter mycobacteriophages (reporter mycobacteriophages), methods of producing said reporter mycobacteriophages and the use of said reporter mycobacteriophages for the rapid diagnosis of mycobacterial infection and the assessment of drug susceptibilities of mycobacterial strains in clinical samples. In particular, this invention is directed to the production and use of luciferase reporter mycobacteriophages to diagnose ***tuberculosis*** . The mycobacterial species-specific reporter mycobacteriophages comprise mycobacterial species-specific mycobacteriophages which contain reporter genes and transcriptional promoters therein. When the reporter mycobacteriophages are incubated with clinical samples which may contain the mycobacteria of interest, the gene product of the reporter genes will be expressed if the sample contains the mycobacteria of interest, thereby diagnosing mycobacterial infection.

AU ***Jacobs, Jr., W.R.*** ; Bloom, B.R.; Hatfull, G.F.

AB . . . in clinical samples. In particular, this invention is directed to the production and use of luciferase reporter mycobacteriophages to diagnose ***tuberculosis*** . The mycobacterial species-specific reporter mycobacteriophages comprise mycobacterial species-specific mycobacteriophages which contain reporter genes and transcriptional promoters therein. When the reporter. . .

UT Reporter gene; ***Tuberculosis*** ; Diagnostic agents; Phages; Patents; Mycobacterium

L2 ANSWER 18 OF 21 LIFESCI COPYRIGHT 2008 CSA on STN

AN 2001:28531 LIFESCI <<LOGINID::20080330>>

TI Thiolactomycin and Related Analogues as Novel Anti- mycobacterial Agents Targeting KasA and KasB Condensing Enzymes in Mycobacterium ***tuberculosis***

AU Kremer, L.; Douglas, J.D.; Baulard, A.R.; Morehouse, C.; Guy, M.R.; Alland, D.; Dover, L.G.; Lakey, J.H.; ***Jacobs Jr., W.R.*** ; Brennan, P.J.; Minnikin, D.E.; Besra, G.S.

CS Departments of Microbiology and Immunology and Chemistry, School of Biochemistry and Genetics, University of Newcastle upon Tyne, Newcastle upon Tyne, NE2 4HH England, INSERM U447, Institut Pasteur de Lille, 59019

Lille, France; E-mail: g.s.besra@newcastle.ac.uk.
SO Journal of Biological Chemistry [J. Biol. Chem.], (20000603) vol. 275, no. 22, pp. 16857-16864.
ISSN: 0021-9258.
DT Journal
FS J
LA English
SL English
AB Prevention efforts and control of ***tuberculosis*** are seriously hampered by the appearance of multidrug- resistant strains of Mycobacterium ***tuberculosis*** , dictating new approaches to the treatment of the disease. Thiolactomycin (TLM) is a unique thiolactone that has been shown to exhibit anti-mycobacterial activity by specifically inhibiting fatty acid and mycolic acid biosynthesis. In this study, we present evidence that TLM targets two beta -ketoacyl-acyl-carrier protein synthases, KasA and KasB, consistent with the fact that both enzymes belong to the fatty-acid synthase type II system involved in fatty acid and mycolic acid biosynthesis. Overexpression of KasA, KasB, and KasAB in Mycobacterium bovis BCG increased in vivo and in vitro resistance against TLM. In addition, a multidrug-resistant clinical isolate was also found to be highly sensitive to TLM, indicating promise in counteracting multidrug-resistant strains of M. ***tuberculosis*** . The design and synthesis of several TLM derivatives have led to compounds more potent both in vitro against fatty acid and mycolic acid biosynthesis and in vivo against M. ***tuberculosis*** . Finally, a three-dimensional structural model of KasA has also been generated to improve understanding of the catalytic site of mycobacterial Kas proteins and to provide a more rational approach to the design of new drugs.
TI Thiolactomycin and Related Analogues as Novel Anti- mycobacterial Agents Targeting KasA and KasB Condensing Enzymes in Mycobacterium ***tuberculosis***
AU Kremer, L.; Douglas, J.D.; Baulard, A.R.; Morehouse, C.; Guy, M.R.; Alland, D.; Dover, L.G.; Lakey, J.H.; ***Jacobs Jr., W.R.*** ; Brennan, P.J.; Minnikin, D.E.; Besra, G.S.
AB Prevention efforts and control of ***tuberculosis*** are seriously hampered by the appearance of multidrug- resistant strains of Mycobacterium ***tuberculosis*** , dictating new approaches to the treatment of the disease. Thiolactomycin (TLM) is a unique thiolactone that has been shown to. . . multidrug-resistant clinical isolate was also found to be highly sensitive to TLM, indicating promise in counteracting multidrug-resistant strains of M. ***tuberculosis*** . The design and synthesis of several TLM derivatives have led to compounds more potent both in vitro against fatty acid and mycolic acid biosynthesis and in vivo against M. ***tuberculosis*** . Finally, a three-dimensional structural model of KasA has also been generated to improve understanding of the catalytic site of mycobacterial. . .
UT ***Tuberculosis*** ; Drug resistance; Overexpression; KasA protein; thiolactomycin; Mycobacterium ***tuberculosis***

L2 ANSWER 19 OF 21 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1998:15665 CAPLUS <<LOGINID::20080330>>
DN 128:99300
TI Crystalline gene inhA enoyl-ACP reductase of Mycobacterium ***tuberculosis***
IN Sacchettini, James; Blanchard, John; ***Jacobs, Jr William R.***
PA Albert Einstein College of Medicine of Yeshiva University, USA
SO U.S., 22 pp.

CODEN: USXXAM
DT Patent
LA English
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5702935	A	19971230	US 1994-234011	19940428
	US 5648392	A	19970715	US 1995-386917	19950207
	US 5556778	A	19960917	US 1995-491146	19950616
	US 5837480	A	19981117	US 1996-700306	19960821
	US 5882878	A	19990316	US 1996-701062	19960821
	US 5837732	A	19981117	US 1996-766273	19961213
PRAI	US 1994-234011	A2	19940428		
	US 1994-307376	B2	19940916		
	US 1995-386917	A2	19950207		
	US 1995-491146	A3	19950616		
	US 1996-598085	B1	19960207		

AB Inha enzyme crystals and methods of growing said crystals are presented. Three crystal forms of the Inha enzyme with discrete unit cell parameters were obtained. The crystals of the Inha enzyme are of sufficient size and quality for x-ray crystallog. detn. of the three dimensional structure of the Inha enzyme in concert with heavy atom derivs. of said crystals. With the three dimensional structure of the Inha enzyme, compds. which inhibit the biochem. activity of the Inha enzyme may be developed. The M. ***tuberculosis*** enoyl-ACP reductase gene inhA was expressed in Escherichia coli. The recombinant enzyme was crystd. and its structure detd. by X-ray crystallog.

TI Crystalline gene inhA enoyl-ACP reductase of Mycobacterium ***tuberculosis***

IN Sacchettini, James; Blanchard, John; ***Jacobs, Jr William R.***

AB . . . structure of the Inha enzyme, compds. which inhibit the biochem. activity of the Inha enzyme may be developed. The M. ***tuberculosis*** enoyl-ACP reductase gene inhA was expressed in Escherichia coli. The recombinant enzyme was crystd. and its structure detd. by X-ray. . .

IT Escherichia coli
(InhA prodn. with recombinant; cryst. gene inhA enoyl-ACP reductase of Mycobacterium ***tuberculosis***)

IT Crystal structure
Mycobacterium ***tuberculosis***
(cryst. gene inhA enoyl-ACP reductase of Mycobacterium ***tuberculosis***)

IT Gene, microbial
RL: BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); USES (Uses)
(inhA; cryst. gene inhA enoyl-ACP reductase of Mycobacterium ***tuberculosis***)

IT 153553-59-4P
RL: BPN (Biosynthetic preparation); PRP (Properties); BIOL (Biological study); PREP (Preparation)
(amino acid sequence; cryst. gene inhA enoyl-ACP reductase of Mycobacterium ***tuberculosis***)

IT 37251-08-4P, Enoyl-ACP reductase
RL: BPN (Biosynthetic preparation); PRP (Properties); BIOL (Biological study); PREP (Preparation)
(cryst. gene inhA enoyl-ACP reductase of Mycobacterium ***tuberculosis***)

IT 162603-45-4, DNA (Mycobacterium ***tuberculosis*** strain H37-Rv gene

inhA plus flanks)
RL: BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); USES (Uses)
(nucleotide sequence; cryst. gene inhA enoyl-ACP reductase of Mycobacterium ***tuberculosis***)

L2 ANSWER 20 OF 21 LIFESCI COPYRIGHT 2008 CSA on STN
AN 97:28104 LIFESCI <<LOGINID::20080330>>
TI Construction of D29 shuttle phasmids and luciferase reporter phages for detection of mycobacteria
AU Pearson, R.E.; Jurgensen, S.; Sarkis, G.J.; Hatfull, G.F.; ***Jacobs*** *** Jr., W.R.***
CS Becton Dickinson Research Center, 21 Davis Drive Research, Triangle Park, NC 27713 USA
SO GENE, (1996) vol. 183, no. 1-2, pp. 129-136.
ISSN: 0378-1119.
DT Journal
FS N; W2
LA English
SL English
AB Diseases caused by Mycobacterium ***tuberculosis*** , M. leprae and M. avium, cause significant morbidity and mortality worldwide. Effective treatments require that the organisms be speciated and that drug susceptibilities for the causative organisms be characterized. Reporter phage technology has been developed as a rapid and convenient method for identifying mycobacterial species and evaluating drug resistance. In this report we describe the construction of luciferase reporter phages from mycobacteriophage D29 DNA. Shuttle phasmids were first constructed with D29 in order to identify non-essential regions of the D29 genomes and to introduce unique cloning sites within that region. Using this approach, we observed that all of the D29 shuttle phasmids had the cosmid vector localized to one area of the phage genome near one cohesive end. These shuttle phasmids had been constructed with a cosmid that could be readily excised from the D29 genome with different sets of restriction enzymes. Luciferase reporter phages were made by substituting the luciferase cassette for the cosmid vector. Recombinant phages with the luciferase cassette fall into two groups. One group produced light and had the expression cassette oriented with the promoter directing transcription away from the cohesive end. In contrast, the other group had the expression cassette in the opposite orientation and failed to produce light during lytic infection, but did produce light in L5 lysogens which are known to repress D29 promoters. These results suggest that a phage promoter of the D29 phage can occlude the expression of a promoter introduced into this region. D29 luciferase reporter phages are capable of detecting low numbers of L5 lysogens like L5 luciferase phages. However, unlike L5 luciferase phages, D29 luciferase phages can readily infect M. ***tuberculosis*** and M. bovis BCG, demonstrating that these phages can be used to evaluate drug susceptibilities of many types of mycobacteria.
AU Pearson, R.E.; Jurgensen, S.; Sarkis, G.J.; Hatfull, G.F.; ***Jacobs*** *** Jr., W.R.***
AB Diseases caused by Mycobacterium ***tuberculosis*** , M. leprae and M. avium, cause significant morbidity and mortality worldwide. Effective treatments require that the organisms be speciated and. . . numbers of L5 lysogens like L5 luciferase phages. However, unlike L5 luciferase phages, D29 luciferase phages can readily infect M. ***tuberculosis*** and M. bovis BCG, demonstrating that these phages can be used to evaluate

drug susceptibilities of many types of mycobacteria.
UT phage D29; luciferase; Mycobacterium ***tuberculosis*** ; shuttle vectors; reporter genes; Mycobacterium leprae; Mycobacterium avium; Mycobacterium bovis

L2 ANSWER 21 OF 21 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1995:442076 CAPLUS <<LOGINID::20080330>>
DN 122:209575
TI Crystal structure and function of the isoniazid target of Mycobacterium ***tuberculosis***
AU Dessen, Andrea; Quemard, Annaik; Blanchard, John S.; ***Jacobs Jr.,*** *** William R.*** ; Sacchettini, James C.
CS Department Biochemistry, Albert Einstein College Medicine, Bronx, NY, 10461, USA
SO Science (Washington, D. C.) (1995), 267(5204), 1638-41
CODEN: SCIEAS; ISSN: 0036-8075
PB American Association for the Advancement of Science
DT Journal
LA English
AB Resistance to isoniazid in Mycobacterium ***tuberculosis*** can be mediated by substitution of alanine for serine 94 in the InhA protein, the drug's primary target. InhA was shown to catalyze the .beta.-NAD (NADH)-specific redn. of 2-trans-enoyl-acyl carrier protein, an essential step in fatty acid elongation. Kinetic analyses suggested that isoniazid resistance is due to a decreased affinity of the mutant protein for NADH. The three-dimensional structures of wild-type and mutant InhA, refined to 2.2 and 2.7 angstroms, resp., revealed that drug resistance is directly related to a perturbation in the hydrogen-bonding network that stabilizes NADH binding.
TI Crystal structure and function of the isoniazid target of Mycobacterium ***tuberculosis***
AU Dessen, Andrea; Quemard, Annaik; Blanchard, John S.; ***Jacobs Jr.,*** *** William R.*** ; Sacchettini, James C.
AB Resistance to isoniazid in Mycobacterium ***tuberculosis*** can be mediated by substitution of alanine for serine 94 in the InhA protein, the drug's primary target. InhA was. . .
IT Mycobacterium ***tuberculosis***
(crystal structure and function of isoniazid target of Mycobacterium ***tuberculosis***)
IT Gene, microbial
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(for InhA protein; crystal structure and function of isoniazid target of Mycobacterium ***tuberculosis***)
IT Amino acids, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(position-94 serine; crystal structure and function of isoniazid target of Mycobacterium ***tuberculosis***)
IT 54-85-3, Isoniazid
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(crystal structure and function of isoniazid target of Mycobacterium ***tuberculosis***)
IT 56-41-7, Alanine, biological studies 56-45-1, Serine, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(position-94; crystal structure and function of isoniazid target of Mycobacterium ***tuberculosis***)

```
=> e hsu tsungda/au
E1          16     HSU TSUNG YUAN/AU
E2           1     HSU TSUNG YUEH/AU
E3          54 --> HSU TSUNGDA/AU
E4           1     HSU TSUNGWEN/AU
E5           1     HSU TSUNGYANG/AU
E6           2     HSU TSWEI FUNG/AU
E7          10     HSU TSZ CHING/AU
E8           4     HSU TUAN CHENG/AU
E9           6     HSU TUAN FU/AU
E10          1     HSU TUAN JUNG/AU
E11          1     HSU TUAN WEI/AU
E12          1     HSU TUAN YEN/AU

=> s e3 and tuberculosis
L3          23 "HSU TSUNGDA"/AU AND TUBERCULOSIS

=> dup rem l3
PROCESSING COMPLETED FOR L3
L4            8 DUP REM L3 (15 DUPLICATES REMOVED)

=> d bib ab kwic 1-
YOU HAVE REQUESTED DATA FROM 8 ANSWERS - CONTINUE? Y/(N):y

L4   ANSWER 1 OF 8  BIOSIS  COPYRIGHT (c) 2008 The Thomson Corporation  on STN
     DUPLICATE 1
AN   2007:587540  BIOSIS <<LOGINID::20080330>>
DN   PREV200700589280
TI   Sulfite reduction in mycobacteria.
AU   Pinto, Rachel; Harrison, Joseph S.;   ***Hsu, Tsungda***  ; Jacobs,
     William R. Jr.; Leyh, Thomas S. [Reprint Author]
CS   Albert Einstein Coll Med, Dept Biochem, 1300 Morris Pk Ave, Bronx, NY
     10461 USA
     leyh@aecom.yu.edu
SO   Journal of Bacteriology, (SEP 2007) Vol. 189, No. 18, pp. 6714-6722.
     CODEN: JOBAAY. ISSN: 0021-9193.
DT   Article
LA   English
ED   Entered STN: 21 Nov 2007
     Last Updated on STN: 21 Nov 2007
AB   Mycobacterium   ***tuberculosis***   places an enormous burden on the
     welfare of humanity.  Its ability to grow and its pathogenicity are linked
     to sulfur metabolism, which is considered a fertile area for the
     development of antibiotics, particularly because many of the sulfur
     acquisition steps in the bacterium are not found in the host.  Sulfite
     reduction is one such mycobacterium-specific step and is the central focus
     of this paper.  Sulfite reduction in Mycobacterium smegmatis was
     investigated using a combination of deletion mutagenesis, metabolite
     screening, complementation, and enzymology.  The initial rate parameters
     for the purified sulfite reductase from M.   ***tuberculosis***   were
     determined under strict anaerobic conditions [k(cat) = 1.0 (+/- 0.1)
     electron consumed per second, and K-m(SO3())-2 = 27 (+/- 1) mu M], and the
     enzyme exhibits no detectible turnover of nitrite, which need not be the
     case in the sulfite/nitrite reductase family.  Deletion of sulfite
     reductase (sirA, originally misannotated nirA) reveals that it is
     essential for growth on sulfate or sulfite as the sole sulfur source and,
```

further, that the nitrite-reducing activities of the cell are incapable of reducing sulfite at a rate sufficient to allow growth. Like their nitrite reductase counterparts, sulfite reductases require a siroheme cofactor for catalysis. Rv2393 (renamed che1) resides in the sulfur reduction operon and is shown for the first time to encode a ferrochelatase, a catalyst that inserts Fe2+ into siroheme. Deletion of che1 causes cells to grow slowly on metabolites that require sulfite reductase activity. This slow-growth phenotype was ameliorated by optimizing growth conditions for nitrite assimilation, suggesting that nitrogen and sulfur assimilation overlap at the point of ferrochelatase synthesis and delivery.

AU Pinto, Rachel; Harrison, Joseph S.; ***Hsu, Tsungda*** ; Jacobs, William R. Jr.; Leyh, Thomas S. [Reprint Author]

AB Mycobacterium ***tuberculosis*** places an enormous burden on the welfare of humanity. Its ability to grow and its pathogenicity are linked to sulfur. . . combination of deletion mutagenesis, metabolite screening, complementation, and enzymology. The initial rate parameters for the purified sulfite reductase from M. ***tuberculosis*** were determined under strict anaerobic conditions [k(cat) = 1.0 (+/- 0.1) electron consumed per second, and K-m(SO3())-2 = 27 (+/-. . .

ORGN Classifier
Mycobacteriaceae 08881
Super Taxa
Mycobacteria; Actinomycetes and Related Organisms; Eubacteria; Bacteria; Microorganisms
Organism Name
Mycobacterium ***tuberculosis*** (species)
Taxa Notes
Bacteria, Eubacteria, Microorganisms

GEN Mycobacterium ***tuberculosis*** sirA gene (Mycobacteriaceae): deletion; Mycobacterium ***tuberculosis*** chel gene (Mycobacteriaceae): sulfur reduction operon

L4 ANSWER 2 OF 8 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN DUPLICATE 2

AN 2007:541735 BIOSIS <<LOGINID::20080330>>

DN PREV200700545827

TI Mycobacterium ***tuberculosis*** nuoG is a virulence gene that inhibits apoptosis of infected host cells.

AU Velmurugan, Kamalakannan; Chen, Bing; Miller, Jessica L.; Azogue, Sharon; Gurses, Serdar; ***Hsu, Tsungda*** ; Glickman, Michael; Jacobs, William R. Jr.; Porcelli, Steven A.; Briken, Volker [Reprint Author]

CS Univ Maryland, Dept Mol Genet and Cell Biol, College Pk, MD 20742 USA
vbriken@umd.edu

SO PLoS Pathogens, (JUL 2007) Vol. 3, No. 7, pp. 972-980.
http://www.plospathogens.org.
ISSN: 1553-7366. E-ISSN: 1553-7374.

DT Article

LA English

ED Entered STN: 17 Oct 2007
Last Updated on STN: 17 Oct 2007

AB The survival and persistence of Mycobacterium ***tuberculosis*** depends on its capacity to manipulate multiple host defense pathways, including the ability to actively inhibit the death by apoptosis of infected host cells. The genetic basis for this anti-apoptotic activity and its implication for mycobacterial virulence have not been demonstrated or elucidated. Using a novel gain-of-function genetic screen, we demonstrated that inhibition of infection-induced apoptosis of macrophages

is controlled by multiple genetic loci in M. ***tuberculosis*** . Characterization of one of these loci in detail revealed that the anti-apoptosis activity was attributable to the type I NADH-dehydrogenase of M. ***tuberculosis*** , and was mainly due to the subunit of this multicomponent complex encoded by the nuoG gene. Expression of M. ***tuberculosis*** nuoG in nonpathogenic mycobacteria endowed them with the ability to inhibit apoptosis of infected human or mouse macrophages, and increased their virulence in a SCID mouse model. Conversely, deletion of nuoG in M. ***tuberculosis*** ablated its ability to inhibit macrophage apoptosis and significantly reduced its virulence in mice. These results identify a key component of the genetic basis for an important virulence trait of M. ***tuberculosis*** and support a direct causal relationship between virulence of pathogenic mycobacteria and their ability to inhibit macrophage apoptosis.

TI Mycobacterium ***tuberculosis*** nuoG is a virulence gene that inhibits apoptosis of infected host cells.

AU Velmurugan, Kamalakannan; Chen, Bing; Miller, Jessica L.; Azogue, Sharon; Gurses, Serdar; ***Hsu, Tsungda*** ; Glickman, Michael; Jacobs, William R. Jr.; Porcelli, Steven A.; Briken, Volker [Reprint Author]

AB The survival and persistence of Mycobacterium ***tuberculosis*** depends on its capacity to manipulate multiple host defense pathways, including the ability to actively inhibit the death by apoptosis. . . gain-of-function genetic screen, we demonstrated that inhibition of infection-induced apoptosis of macrophages is controlled by multiple genetic loci in M. ***tuberculosis*** . Characterization of one of these loci in detail revealed that the anti-apoptosis activity was attributable to the type I NADH-dehydrogenase of M. ***tuberculosis*** , and was mainly due to the subunit of this multicomponent complex encoded by the nuoG gene. Expression of M. ***tuberculosis*** nuoG in nonpathogenic mycobacteria endowed them with the ability to inhibit apoptosis of infected human or mouse macrophages, and increased their virulence in a SCID mouse model. Conversely, deletion of nuoG in M. ***tuberculosis*** ablated its ability to inhibit macrophage apoptosis and significantly reduced its virulence in mice. These results identify a key component of the genetic basis for an important virulence trait of M. ***tuberculosis*** and support a direct causal relationship between virulence of pathogenic mycobacteria and their ability to inhibit macrophage apoptosis.

ORGN . . .
Mammals, Rodents, Vertebrates

ORGN Classifier
Mycobacteriaceae 08881

Super Taxa
Mycobacteria; Actinomycetes and Related Organisms; Eubacteria; Bacteria; Microorganisms

Organism Name
Mycobacterium ***tuberculosis*** (species): pathogen
Mycobacterium smegmatis (species)
Mycobacterium kansasii (species): strain-Hauduroy

Taxa Notes
Bacteria, Eubacteria, Microorganisms

GEN Mycobacterium ***tuberculosis*** nuoG gene [Mycobacterium ***tuberculosis*** NADH dehydrogenase I gene] (Mycobacteriaceae)

L4 ANSWER 3 OF 8 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
DUPLICATE 3

AN 2007:104150 BIOSIS <<LOGINID::20080330>>

DN PREV200700101279
TI Characterization of the protective T-cell response generated in CD4-deficient mice by a live attenuated Mycobacterium ***tuberculosis*** vaccine.
AU Derrick, Steven C. [Reprint Author]; Evering, Teresa H.; Sambandamurthy, Vasan K.; Jalapathy, Kripa V.; ***Hsu, Tsungda*** ; Chen, Bing; Chen, Mei; Russell, Robert G.; Junqueira-Kipnis, Ana Paula; Orme, Ian M.; Porcelli, Steven A.; Jacobs, William R. Jr.; Morris, Sheldon L.
CS NINCDS, Ctr Biol Evaluat and Res, Bldg 10, Bethesda, MD 20892 USA steven.derrick@fda.hhs.gov; Jacobsw@hhmi.org
SO Immunology, (FEB 2007) Vol. 120, No. 2, pp. 192-206.
CODEN: IMMUAM. ISSN: 0019-2805.
DT Article
LA English
ED Entered STN: 7 Feb 2007
Last Updated on STN: 7 Feb 2007
AB The global epidemic of ***tuberculosis*** , fuelled by acquired immune-deficiency syndrome, necessitates the development of a safe and effective vaccine. We have constructed a Delta RD1 Delta panCD mutant of Mycobacterium ***tuberculosis*** (mc(2)6030) that undergoes limited replication and is severely attenuated in immunocompromised mice, yet induces significant protection against ***tuberculosis*** in wild-type mice and even in mice that completely lack CD4(+) T cells as a result of targeted disruption of their CD4 genes (CD4(-/-) mice). Ex vivo studies of T cells from mc(2)6030-immunized mice showed that these immune cells responded to protein antigens of M. ***tuberculosis*** in a major histocompatibility complex (MHC) class II-restricted manner. Antibody depletion experiments showed that antituberculosis protective responses in the lung were not diminished by removal of CD8(+), T-cell receptor gamma delta (TCR-gamma delta(+)) and NK1.1(+) T cells from vaccinated CD4(-/-) mice before challenge, implying that the observed recall and immune effector functions resulting from vaccination of CD4(-/-) mice with mc(2)6030 were attributable to a population of CD4(-) CD8(-) (double-negative) TCR-alpha beta(+), TCR-gamma delta(-), NK1.1(-) T cells. Transfer of highly enriched double-negative TCR-alpha beta(+) T cells from mc(2)6030-immunized CD4(-/-) mice into naive CD4(-/-) mice resulted in significant protection against an aerosol ***tuberculosis*** challenge. Enriched pulmonary double-negative T cells transcribed significantly more interferon-gamma and interleukin-2 mRNA than double-negative T cells from naive mice after a tuberculous challenge. These results confirmed previous findings on the potential for a subset of MHC class II-restricted T cells to develop and function without expression of CD4 and suggest novel vaccination strategies to assist in the control of ***tuberculosis*** in human immunodeficiency virus-infected humans who have chronic depletion of their CD4(+) T cells.
TI Characterization of the protective T-cell response generated in CD4-deficient mice by a live attenuated Mycobacterium ***tuberculosis*** vaccine.
AU Derrick, Steven C. [Reprint Author]; Evering, Teresa H.; Sambandamurthy, Vasan K.; Jalapathy, Kripa V.; ***Hsu, Tsungda*** ; Chen, Bing; Chen, Mei; Russell, Robert G.; Junqueira-Kipnis, Ana Paula; Orme, Ian M.; Porcelli, Steven A.; Jacobs, William R.. . .
AB The global epidemic of ***tuberculosis*** , fuelled by acquired immune-deficiency syndrome, necessitates the development of a safe and effective vaccine. We have constructed a Delta RD1 Delta panCD mutant of Mycobacterium ***tuberculosis*** (mc(2)6030) that undergoes limited replication and is severely attenuated in immunocompromised mice, yet

induces significant protection against ***tuberculosis*** in wild-type mice and even in mice that completely lack CD4(+) T cells as a result of targeted disruption of. . . Ex vivo studies of T cells from mc(2)6030-immunized mice showed that these immune cells responded to protein antigens of M. ***tuberculosis*** in a major histocompatibility complex (MHC) class II-restricted manner. Antibody depletion experiments showed that antituberculosis protective responses in the lung. . . double-negative TCR-alpha beta(+) T cells from mc(2)6030-immunized CD4(-/-) mice into naive CD4(-/-) mice resulted in significant protection against an aerosol ***tuberculosis*** challenge. Enriched pulmonary double-negative T cells transcribed significantly more interferon-gamma and interleukin-2 mRNA than double-negative T cells from naive mice. . . cells to develop and function without expression of CD4 and suggest novel vaccination strategies to assist in the control of ***tuberculosis*** in human immunodeficiency virus-infected humans who have chronic depletion of their CD4(+) T cells.

IT . . .
immune cell: immune system; T-cell: immune system, blood and lymphatics; natural killer cell: immune system, blood and lymphatics

IT Diseases
tuberculosis : bacterial disease, infectious disease, immune system disease, drug therapy
Tuberculosis (MeSH)

IT Chemicals & Biochemicals
messenger RNA [mRNA]; interleukin-2 [IL-2]; CD8; CD4; major histocompatibility complex class II [MHC class II];. . .

ORGN . . .
Mammals, Rodents, Vertebrates

ORGN Classifier
Mycobacteriaceae 08881

Super Taxa
Mycobacteria; Actinomycetes and Related Organisms; Eubacteria; Bacteria; Microorganisms

Organism Name
Mycobacterium ***tuberculosis*** (species): pathogen, strain-H37Rv, strain-Erdman

Taxa Notes
Bacteria, Eubacteria, Microorganisms

L4 ANSWER 4 OF 8 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
DUPLICATE 4

AN 2006:614816 BIOSIS <<LOGINID::20080330>>

DN PREV200600621274

TI Mycobacterium ***tuberculosis*** Delta RD1 Delta panCD: A safe and limited replicating mutant strain that protects immunocompetent and immunocompromised mice against experimental ***tuberculosis*** .

AU Sambandamurthy, Vasan K. [Reprint Author]; Derrick, Steven C.; ***Hsu,*** ***Tsungda*** ; Chen, Bing; Larsen, Michelle H.; Jalapathy, Kripa V.; Chen, Mei; Kim, John; Porcelli, Steven A.; Chan, John; Morris, Sheldon L.; Jacobs, William R. Jr.

CS US FDA, Ctr Biol Evaluat and Res, Bethesda, MD 20892 USA
jacobsw@hhmi.org

SO Vaccine, (SEP 11 2006) Vol. 24, No. 37-39, pp. 6309-6320.
CODEN: VACCDE. ISSN: 0264-410X.

DT Article

LA English
ED Entered STN: 15 Nov 2006
Last Updated on STN: 15 Nov 2006
AB The global epidemic of ***tuberculosis*** (TB), fueled by the growing HIV pandemic, warrants the development of a safe and effective vaccine against TB. We report the construction and characterization of an unlinked double deletion mutant of Mycobacterium ***tuberculosis*** H37Rv that deletes both the primary attenuating mutation of BCG (Delta RD1) and two genes required for the synthesis of pantothenate (Delta panCD). The M. ***tuberculosis*** Delta RD1 Delta panCD (mc(2)6030) mutant undergoes limited replication in mice, and yet is both significantly safer than BCG in immunocompromised mice and also safe in guinea pigs. Additionally, the mc(2)6030 strain does not reactivate in a mouse chemo-immunosuppression model. Importantly, long-lived protective immune responses following immunization with the mc(2)6030 strain prolong the survival of wild type mice, and CD4-deficient mice against an aerosol challenge with virulent M. ***tuberculosis*** . Given its overall safety and effectiveness, the mc(2)6030 live attenuated strain should be considered as a human vaccine candidate for protecting both healthy and HIV-infected individuals against TB. (c) 2006 Elsevier Ltd. All rights reserved.
TI Mycobacterium ***tuberculosis*** Delta RD1 Delta panCD: A safe and limited replicating mutant strain that protects immunocompetent and immunocompromised mice against experimental ***tuberculosis*** .
AU Sambandamurthy, Vasan K. [Reprint Author]; Derrick, Steven C.; ***Hsu,*** *** Tsungda*** ; Chen, Bing; Larsen, Michelle H.; Jalapathy, Kripa V.; Chen,
Mei; Kim, John; Porcelli, Steven A.; Chan, John; Morris, Sheldon. . .
AB The global epidemic of ***tuberculosis*** (TB), fueled by the growing HIV pandemic, warrants the development of a safe and effective vaccine against TB. We report the construction and characterization of an unlinked double deletion mutant of Mycobacterium ***tuberculosis*** H37Rv that deletes both the primary attenuating mutation of BCG (Delta RD1) and two genes required for the synthesis of pantothenate (Delta panCD). The M. ***tuberculosis*** Delta RD1 Delta panCD (mc(2)6030) mutant undergoes limited replication in mice, and yet is both significantly safer than BCG in. . . the mc(2)6030 strain prolong the survival of wild type mice, and CD4-deficient mice against an aerosol challenge with virulent M. ***tuberculosis*** . Given its overall safety and effectiveness, the mc(2)6030 live attenuated strain should be considered as a human vaccine candidate for. . .
IT Major Concepts
Pharmacology; Infection; Immune System (Chemical Coordination and Homeostasis)
IT Diseases
experimental ***tuberculosis*** : bacterial disease, infectious disease, prevention and control
IT Chemicals & Biochemicals
CD4; ***tuberculosis*** vaccine: immunologic-drug, immunostimulant-drug
ORGN . . .
Mammals, Rodents, Vertebrates
ORGN Classifier
Mycobacteriaceae 08881
Super Taxa
Mycobacteria; Actinomycetes and Related Organisms; Eubacteria; Bacteria; Microorganisms

Organism Name
Mycobacterium ***tuberculosis*** (species): pathogen, strain-H37Rv, strain-delta-RD1, strain-delta-panCD, strain-mc-2-6030, strain-BCG Pasteur, strain-Erdman
Taxa Notes
Bacteria, Eubacteria, Microorganisms
ORGN Classifier
Retroviridae 03305
Super Taxa

L4 ANSWER 5 OF 8 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
DUPLICATE 5
AN 2006:613959 BIOSIS <<LOGINID::20080330>>
DN PREV200600610605
TI Mycobacteria lacking the RD1 region do not induce necrosis in the lungs of mice lacking interferon-gamma.
AU Junqueira-Kipnis, Ana Paula; Basaraba, Randall J.; Gruppo, Veronica; Palanisamy, Gopinath; Turner, Oliver C.; ***Hsu, Tsungda*** ; Jacobs, William R. Jr.; Fulton, Scott A.; Reba, Scott M.; Boom, W. Henry; Orme, Ian M. [Reprint Author]
CS Colorado State Univ, Dept Microbiol Immunol and Pathol, Mycobacteria Res Labs, Ft Collins, CO 80523 USA
ian.orme@colostate.edu
SO Immunology, (OCT 2006) Vol. 119, No. 2, pp. 224-231.
CODEN: IMMUAM. ISSN: 0019-2805.
DT Article
LA English
ED Entered STN: 15 Nov 2006
Last Updated on STN: 15 Nov 2006
AB The genetic region of difference 1 (RD1) in Mycobacterium ***tuberculosis*** has recently been hypothesized to encode for proteins that are cytotoxic to the host cell in nature. We demonstrate here that while M. ***tuberculosis*** grew progressively in the lungs of gene disrupted mice (GKO) unable to produce interferon-gamma (IFN-gamma), similar mice infected instead with M. bovis bacillus Calmette-Guerin (BCG) reproducibly exhibited an obvious slowing of the disease after about 20 days. Closer examination of BCG-infected GKO mice showed a florid granulomatous inflammation in the lungs, whereas similar mice infected with M. ***tuberculosis*** exhibited wholesale progressive necrosis. In the BCG-infected GKO mice large numbers of activated effector T cells, some strongly positive for the cytokine tumour necrosis factor, as well as activated natural killer cells accumulated in the lungs. To further test the hypothesis that the differences observed were directly associated with the loss of the RD1 region, it was then shown that a mutant of M. ***tuberculosis*** lacking RD1 grew progressively in both normal and GKO mice but failed to induce any degree of necrosis in either animal despite reaching similar levels in the lungs. However, when mice were infected with this mutant, in which the RD1 region had been restored by complementation, wholesale necrosis of the lungs again occurred. These data support the hypothesis that proteins encoded in the RD1 region are a major cause of necrosis and contribute significantly to the pathogenesis of the disease.
AU Junqueira-Kipnis, Ana Paula; Basaraba, Randall J.; Gruppo, Veronica; Palanisamy, Gopinath; Turner, Oliver C.; ***Hsu, Tsungda*** ; Jacobs, William R. Jr.; Fulton, Scott A.; Reba, Scott M.; Boom, W. Henry; Orme,

Ian M. [Reprint Author]
AB The genetic region of difference 1 (RD1) in Mycobacterium ***tuberculosis*** has recently been hypothesized to encode for proteins that are cytotoxic to the host cell in nature. We demonstrate here that while M. ***tuberculosis*** grew progressively in the lungs of gene disrupted mice (GKO) unable to produce interferon-gamma (IFN-gamma), similar mice infected instead with. . . Closer examination of BCG-infected GKO mice showed a florid granulomatous inflammation in the lungs, whereas similar mice infected with M. ***tuberculosis*** exhibited wholesale progressive necrosis. In the BCG-infected GKO mice large numbers of activated effector T cells, some strongly positive for. . . observed were directly associated with the loss of the RD1 region, it was then shown that a mutant of M. ***tuberculosis*** lacking RD1 grew progressively in both normal and GKO mice but failed to induce any degree of necrosis in either. . .
IT . . .
IT Parts, Structures, & Systems of Organisms
T cell: immune system, blood and lymphatics; lung: respiratory system
IT Diseases
Mycobacterium ***tuberculosis*** infection: respiratory system disease, infectious disease, bacterial disease, genetics, immunology
IT Chemicals & Biochemicals
interferon-gamma [IFN-gamma]
ORGN . . .
Mammals, Rodents, Vertebrates
ORGN Classifier
Mycobacteriaceae 08881
Super Taxa
Mycobacteria; Actinomycetes and Related Organisms; Eubacteria; Bacteria; Microorganisms
Organism Name
Mycobacterium ***tuberculosis*** (species): pathogen
Mycobacterium bovis (species): pathogen
Taxa Notes
Bacteria, Eubacteria, Microorganisms

L4 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2004:648328 CAPLUS <<LOGINID::20080330>>
DN 141:172863
TI Mycobacterial vaccine comprising deletion mutagenesis in RD1 region, and vitamin and amino acid production-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes
IN Bardarov, Stoyan; Jacobs, William R., Jr.; ***Hsu, Tsungda*** ; Sambandamurthy, Vasan; Morris, Sheldon
PA Albert Einstein College of Medicine of Yeshiva University, USA
SO PCT Int. Appl., 116 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004066928	A2	20040812	WO 2004-US1773	20040123
WO 2004066928	A3	20060105		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,

GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW,
MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

US 2007202131 A1 20070830 US 2007-542958 20070130

PRAI US 2003-442631P P 20030124

WO 2004-US1773 W 20040123

AB Methods of treating a mammal that is deficient in CD4+ and/or CD8+ lymphocytes are provided. The methods comprise inoculating the mammal with an attenuated mycobacterium in the M. ***tuberculosis*** complex. In these methods, the mycobacterium comprises two deletions, wherein a virulent mycobacterium in the M. ***tuberculosis*** complex having either deletion exhibits attenuated virulence. The two deletions is a deletion of RD1 region, region controlling prodn. of vitamin (e.g. pantothenic acid or NAD), and region controlling prodn. of amino acid (e.g. proline, tryptophan, leucine, or lysin). The deletion is .DELTA.panCD deletion and .DELTA.lysA deletion. Use of these mycobacteria for the manuf. of a medicament for the treatment of mammals deficient in CD4+ and/or CD8+ lymphocytes is also provided.

IN Bardarov, Stoyan; Jacobs, William R., Jr.; ***Hsu, Tsungda*** ; Sambandamurthy, Vasan; Morris, Sheldon

AB . . . in CD4+ and/or CD8+ lymphocytes are provided. The methods comprise inoculating the mammal with an attenuated mycobacterium in the M. ***tuberculosis*** complex. In these methods, the mycobacterium comprises two deletions, wherein a virulent mycobacterium in the M. ***tuberculosis*** complex having either deletion exhibits attenuated virulence. The two deletions is a deletion of RD1 region, region controlling prodn. of. . .

ST Mycobacterium ***tuberculosis*** complex deletion RD1 vitamin amino acid prodn; mycobacterial vaccine RD1 panCD lysA deletion CD4 CD8 lymphocyte

IT Mycobacterium ***tuberculosis***
(H37Rv and CDC1551 strains; mycobacterial vaccine comprising deletion mutagenesis in RD1 region, and vitamin and amino acid prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

IT Borrelia
Bos taurus
CD4-positive T cell
CD8-positive T cell
DNA sequences
Genetic engineering
Herpesviridae
Human
Human herpesvirus
Human immunodeficiency virus
Human poliovirus
Immunostimulants
Leishmania
Mammalia
Measles virus
Molecular cloning
Mumps virus

Mycobacterium
Mycobacterium africanum
Mycobacterium avium
Mycobacterium bovis
Mycobacterium intracellulare
Mycobacterium leprae
Neisseria
Pertussis
Rabies virus
Salmonella
Shigella
Transduction, genetic
Treponema
Tuberculosis
Vibrio cholerae
(mycobacterial vaccine comprising deletion mutagenesis in RD1 region, and vitamin and amino acid prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

L4 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2003:678598 CAPLUS <<LOGINID::20080330>>
DN 139:212868
TI Attenuated Mycobacterium ***tuberculosis*** vaccines comprising deletion of RD1 region
IN Jacobs, William R., Jr.; ***Hsu, Tsungda*** ; Bardarov, Stoyan; Sambandamurthy, Vasan
PA Albert Einstein College of Medicine of Yeshiva University, USA
SO PCT Int. Appl., 102 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003070164	A2	20030828	WO 2003-US2046	20030124
	WO 2003070164	A3	20060216		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	AU 2003209345	A1	20030909	AU 2003-209345	20030124
PRAI	US 2002-358152P	P	20020219		
	WO 2003-US2046	W	20030124		

AB Non-naturally occurring mycobacteria in the Mycobacterium ***tuberculosis*** complex are provided. These mycobacteria have a deletion of an RD1 region or a region controlling prodn. of a vitamin, and exhibit attenuated virulence in a mammal when compared to the mycobacteria without the deletion. Also provided are non-naturally occurring mycobacteria that have a deletion of a region controlling prodn. of lysine, and mycobacteria comprising two attenuating deletions. Vaccines comprising these mycobacteria are also provided, as are methods of

protecting mammals from virulent mycobacteria using the vaccines. Also provided are methods of prepg. these vaccines which include the step of deleting an RD1 region or a region controlling prodn. of a vitamin from a mycobacterium in the M ***tuberculosis*** complex.

TI Attenuated Mycobacterium ***tuberculosis*** vaccines comprising deletion of RD1 region

IN Jacobs, William R., Jr.; ***Hsu, Tsungda*** ; Bardarov, Stoyan; Sambandamurthy, Vasan

AB Non-naturally occurring mycobacteria in the Mycobacterium ***tuberculosis*** complex are provided. These mycobacteria have a deletion of an RD1 region or a region controlling prodn. of a vitamin,. . . step of deleting an RD1 region or a region controlling prodn. of a vitamin from a mycobacterium in the M ***tuberculosis*** complex.

ST Mycobacterium ***tuberculosis*** vitamin pantothenic acid NAD RD1 region deletion; antigen vaccine Mycobacterium ***tuberculosis*** RD1 deletion

IT Borrelia
Bos taurus
DNA sequences
Genetic engineering
Genetic markers
Herpesviridae
Human
Human immunodeficiency virus
Human poliovirus
Immunodeficiency
Immunostimulants
Infection
Leishmania
Mammalia
Measles virus
Molecular cloning
Mumps virus
Mus
Mycobacterium BCG
Mycobacterium africanum
Mycobacterium avium
Mycobacterium bovis
Mycobacterium intracellulare
Mycobacterium leprae
Mycobacterium ***tuberculosis***
Neisseria
Pertussis
Rabies
Recombination, genetic
Salmonella
Shigella
Transduction, genetic
Treponema
Vaccines
Vibrio cholerae
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Vitamins
RL: BSU (Biological study, unclassified); REM (Removal or disposal); BIOL (Biological study); PROC (Process)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of

RD1 region for vaccine prepns.)
IT Antigens
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)
IT Enzymes, biological studies
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)
IT Interleukin 1
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)
IT Interleukin 2
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)
IT Interleukin 3
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)
IT Interleukin 4
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)
IT Interleukin 5
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)
IT Interleukin 6
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)
IT Interleukin 7
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)
IT Lymphokines
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)
IT Lymphotoxin
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)
IT Reporter gene

RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Tumor necrosis factors
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Microorganism
(auxotrophic; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Development, mammalian postnatal
(child; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Toxoids
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(diphtheria; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Steroids, biological studies
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(enzyme; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Drug delivery systems
(injections, s.c.; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Venoms
(insect; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Drug delivery systems
(intradermal; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Development, microbial
(merozoite, malaria; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT DNA
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(recombinant; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Gene, microbial
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(sacB; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Mutagenesis
(site-directed, deletion; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Venoms
(snake; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Development, microbial
(sporozoite, malaria; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Toxoids

RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tetanus; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT ***Tuberculosis***
(vaccine; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Insecta
(venom; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Interferons
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.alpha.; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Interferons
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.beta.; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Interferons
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.gamma.; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT 53-84-9, Nicotinamide adenine dinucleotide 56-87-1, L-Lysine, biological studies 61-90-5, L-Leucine, biological studies 73-22-3, L-Tryptophan, biological studies 79-83-4, Pantothenic acid 147-85-3, L-Proline, biological studies
RL: BSU (Biological study, unclassified); REM (Removal or disposal); BIOL (Biological study); PROC (Process)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT 9001-45-0, .beta. Glucuronidase 9014-00-0, Luciferase 9031-11-2, .beta. Galactosidase 63774-46-9
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT 588746-25-2P
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(nucleotide sequence; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT 588746-26-3 588746-27-4 588746-28-5
RL: BSU (Biological study, unclassified); PRP (Properties); REM (Removal or disposal); BIOL (Biological study); PROC (Process)
(nucleotide sequence; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT 588747-89-1 588747-90-4 588747-91-5 588747-92-6 588747-93-7 588747-94-8 588747-95-9 588747-96-0
RL: PRP (Properties)
(unclaimed nucleotide sequence; attenuated Mycobacterium ***tuberculosis*** vaccines comprising deletion of RD1 region)

L4 ANSWER 8 OF 8 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN

DUPLICATE 6
AN 2003:578657 BIOSIS <<LOGINID::20080330>>
DN PREV200300584283
TI The primary mechanism of attenuation of bacillus Calmette-Guerin is a loss of secreted lytic function required for invasion of lung interstitial tissue.
AU ***Hsu, Tsungda*** ; Hingley-Wilson, Suzanne M.; Chen, Bing; Chen, Mei; Dai, Annie Z.; Morin, Paul M.; Marks, Carolyn B.; Padiyar, Jeevan; Goulding, Celia; Gingery, Mari; Eisenberg, David; Russell, Robert G.; Derrick, Steven C.; Collins, Frank M.; Morris, Sheldon L.; King, C. Harold; Jacobs, William R. Jr. [Reprint Author]
CS Department of Pathology, Howard Hughes Medical Institute, Albert Einstein College of Medicine, Bronx, NY, 10461, USA
jacobsw@hhmi.org
SO Proceedings of the National Academy of Sciences of the United States of America, (October 14 2003) Vol. 100, No. 21, pp. 12420-12425. print.
ISSN: 0027-8424 (ISSN print).
DT Article
LA English
ED Entered STN: 10 Dec 2003
Last Updated on STN: 10 Dec 2003
AB ***Tuberculosis*** remains a leading cause of death worldwide, despite the availability of effective chemotherapy and a vaccine. Bacillus Calmette-Guerin (BCG), the ***tuberculosis*** vaccine, is an attenuated mutant of Mycobacterium bovis that was isolated after serial subcultures, yet the functional basis for this attenuation has never been elucidated. A single region (RD1), which is absent in all BCG substrains, was deleted from virulent M. bovis and Mycobacterium ***tuberculosis*** strains, and the resulting DELTARD1 mutants were significantly attenuated for virulence in both immunocompromised and immunocompetent mice. The M. ***tuberculosis*** DELTARD1 mutants were also shown to protect mice against aerosol challenge, in a similar manner to BCG. Interestingly, the DELTARD1 mutants failed to cause cytolysis of pneumocytes, a phenotype that had been previously used to distinguish virulent M. ***tuberculosis*** from BCG. A specific transposon mutation, which disrupts the Rv3874 Rv3875 (cfp-10 esat-6) operon of RD1, also caused loss of the cytolytic phenotype in both pneumocytes and macrophages. This mutation resulted in the attenuation of virulence in mice, as the result of reduced tissue invasiveness. Moreover, specific deletion of each transcriptional unit of RD1 revealed that three independent transcriptional units are required for virulence, two of which are involved in the secretion of ESAT-6 (6-kDa early secretory antigenic target). We conclude that the primary attenuating mechanism of bacillus Calmette-Guerin is the loss of cytolytic activity mediated by secreted ESAT-6, which results in reduced tissue invasiveness.
AU ***Hsu, Tsungda*** ; Hingley-Wilson, Suzanne M.; Chen, Bing; Chen, Mei; Dai, Annie Z.; Morin, Paul M.; Marks, Carolyn B.; Padiyar, Jeevan; Goulding,. . .
AB ***Tuberculosis*** remains a leading cause of death worldwide, despite the availability of effective chemotherapy and a vaccine. Bacillus Calmette-Guerin (BCG), the ***tuberculosis*** vaccine, is an attenuated mutant of Mycobacterium bovis that was isolated after serial subcultures, yet the functional basis for this. . . elucidated. A single region (RD1), which is absent in all BCG substrains, was deleted from virulent M. bovis and Mycobacterium ***tuberculosis*** strains, and the resulting DELTARD1 mutants were significantly attenuated for virulence in both immunocompromised and immunocompetent mice. The M.

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       ***tuberculosis***   DELTARD1 mutants were also shown to protect mice
     against aerosol challenge, in a similar manner to BCG.  Interestingly, the
     DELTARD1 mutants failed to cause cytolysis of pneumocytes, a phenotype
     that had been previously used to distinguish virulent M.
       ***tuberculosis***   from BCG.  A specific transposon mutation, which
     disrupts the Rv3874 Rv3875 (cfp-10 esat-6) operon of RD1, also caused loss
     of.  .  .
IT   .  .  .
        Infection; Pharmaceuticals (Pharmacology); Respiratory System
        (Respiration)
IT   Parts, Structures, & Systems of Organisms
        lung: respiratory system, interstitial tissue
IT   Diseases
             ***tuberculosis***  : bacterial disease
             ***Tuberculosis***   (MeSH)
IT   Chemicals & Biochemicals
        BCG: vaccine
ORGN .  .  .
ORGN Classifier
        Mycobacteriaceae   08881
     Super Taxa
        Mycobacteria; Actinomycetes and Related Organisms; Eubacteria;
        Bacteria; Microorganisms
     Organism Name
        Mycobacterium bovis (species): pathogen
        Mycobacterium   ***tuberculosis***   (species): pathogen
     Taxa Notes
        Bacteria, Eubacteria, Microorganisms


=> e sambandamurthy vasan/au
E1            1     SAMBANDAMURTHY V/AU
E2            5     SAMBANDAMURTHY V K/AU
E3            6 --> SAMBANDAMURTHY VASAN/AU
E4           26     SAMBANDAMURTHY VASAN K/AU
E5            2     SAMBANDAN ARIVAZHAGAN/AU
E6            4     SAMBANDAN DEEPA/AU
E7            2     SAMBANDAN G/AU
E8           18     SAMBANDAN K/AU
E9            2     SAMBANDAN PRIYA G/AU
E10          14     SAMBANDAN S/AU
E11           1     SAMBANDAN S S/AU
E12           9     SAMBANDAN SANJIV/AU

=> s e1-e4 and tuberculosis
L5           38 ("SAMBANDAMURTHY V"/AU OR "SAMBANDAMURTHY V K"/AU OR "SAMBANDAMU
                RTHY VASAN"/AU OR "SAMBANDAMURTHY VASAN K"/AU) AND TUBERCULOSIS

=> dup rem l5
PROCESSING COMPLETED FOR L5
L6            12 DUP REM L5 (26 DUPLICATES REMOVED)

=> d bib ab kwic 1-
YOU HAVE REQUESTED DATA FROM 12 ANSWERS - CONTINUE? Y/(N):y

L6   ANSWER 1 OF 12  BIOSIS  COPYRIGHT (c) 2008 The Thomson Corporation  on STN
     DUPLICATE 1
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AN 2007:104150 BIOSIS <<LOGINID::20080330>>
DN PREV200700101279
TI Characterization of the protective T-cell response generated in CD4-deficient mice by a live attenuated Mycobacterium ***tuberculosis*** vaccine.
AU Derrick, Steven C. [Reprint Author]; Evering, Teresa H.; ***Sambandamurthy, Vasan K.*** ; Jalapathy, Kripa V.; Hsu, Tsungda; Chen, Bing; Chen, Mei; Russell, Robert G.; Junqueira-Kipnis, Ana Paula; Orme, Ian M.; Porcelli, Steven A.; Jacobs, William R. Jr.; Morris, Sheldon L.
CS NINCDS, Ctr Biol Evaluat and Res, Bldg 10, Bethesda, MD 20892 USA steven.derrick@fda.hhs.gov; Jacobsw@hhmi.org
SO Immunology, (FEB 2007) Vol. 120, No. 2, pp. 192-206. CODEN: IMMUAM. ISSN: 0019-2805.
DT Article
LA English
ED Entered STN: 7 Feb 2007
Last Updated on STN: 7 Feb 2007
AB The global epidemic of ***tuberculosis*** , fuelled by acquired immune-deficiency syndrome, necessitates the development of a safe and effective vaccine. We have constructed a Delta RD1 Delta panCD mutant of Mycobacterium ***tuberculosis*** (mc(2)6030) that undergoes limited replication and is severely attenuated in immunocompromised mice, yet induces significant protection against ***tuberculosis*** in wild-type mice and even in mice that completely lack CD4(+) T cells as a result of targeted disruption of their CD4 genes (CD4(-/-) mice). Ex vivo studies of T cells from mc(2)6030-immunized mice showed that these immune cells responded to protein antigens of M. ***tuberculosis*** in a major histocompatibility complex (MHC) class II-restricted manner. Antibody depletion experiments showed that antituberculosis protective responses in the lung were not diminished by removal of CD8(+), T-cell receptor gamma delta (TCR-gamma delta(+)) and NK1.1(+) T cells from vaccinated CD4(-/-) mice before challenge, implying that the observed recall and immune effector functions resulting from vaccination of CD4(-/-) mice with mc(2)6030 were attributable to a population of CD4(-) CD8(-) (double-negative) TCR-alpha beta(+), TCR-gamma delta(-), NK1.1(-) T cells. Transfer of highly enriched double-negative TCR-alpha beta(+) T cells from mc(2)6030-immunized CD4(-/-) mice into naive CD4(-/-) mice resulted in significant protection against an aerosol ***tuberculosis*** challenge. Enriched pulmonary double-negative T cells transcribed significantly more interferon-gamma and interleukin-2 mRNA than double-negative T cells from naive mice after a tuberculous challenge. These results confirmed previous findings on the potential for a subset of MHC class II-restricted T cells to develop and function without expression of CD4 and suggest novel vaccination strategies to assist in the control of ***tuberculosis*** in human immunodeficiency virus-infected humans who have chronic depletion of their CD4(+) T cells.
TI Characterization of the protective T-cell response generated in CD4-deficient mice by a live attenuated Mycobacterium ***tuberculosis*** vaccine.
AU Derrick, Steven C. [Reprint Author]; Evering, Teresa H.; ***Sambandamurthy, Vasan K.*** ; Jalapathy, Kripa V.; Hsu, Tsungda; Chen, Bing; Chen, Mei; Russell, Robert G.; Junqueira-Kipnis, Ana Paula; Orme, Ian M.;. . .
AB The global epidemic of ***tuberculosis*** , fuelled by acquired immune-deficiency syndrome, necessitates the development of a safe and

effective vaccine. We have constructed a Delta RD1 Delta panCD mutant of Mycobacterium ***tuberculosis*** (mc(2)6030) that undergoes limited replication and is severely attenuated in immunocompromised mice, yet induces significant protection against ***tuberculosis*** in wild-type mice and even in mice that completely lack CD4(+) T cells as a result of targeted disruption of. . . Ex vivo studies of T cells from mc(2)6030-immunized mice showed that these immune cells responded to protein antigens of M. ***tuberculosis*** in a major histocompatibility complex (MHC) class II-restricted manner. Antibody depletion experiments showed that antituberculosis protective responses in the lung. . . double-negative TCR-alpha beta(+) T cells from mc(2)6030-immunized CD4(-/-) mice into naive CD4(-/-) mice resulted in significant protection against an aerosol ***tuberculosis*** challenge. Enriched pulmonary double-negative T cells transcribed significantly more interferon-gamma and interleukin-2 mRNA than double-negative T cells from naive mice. . . cells to develop and function without expression of CD4 and suggest novel vaccination strategies to assist in the control of ***tuberculosis*** in human immunodeficiency virus-infected humans who have chronic depletion of their CD4(+) T cells.

IT . . .
immune cell: immune system; T-cell: immune system, blood and lymphatics; natural killer cell: immune system, blood and lymphatics

IT Diseases
tuberculosis : bacterial disease, infectious disease, immune system disease, drug therapy
Tuberculosis (MeSH)

IT Chemicals & Biochemicals
messenger RNA [mRNA]; interleukin-2 [IL-2]; CD8; CD4; major histocompatibility complex class II [MHC class II];. . .

ORGN . . .
Mammals, Rodents, Vertebrates

ORGN Classifier
Mycobacteriaceae 08881

Super Taxa
Mycobacteria; Actinomycetes and Related Organisms; Eubacteria; Bacteria; Microorganisms

Organism Name
Mycobacterium ***tuberculosis*** (species): pathogen, strain-H37Rv, strain-Erdman

Taxa Notes
Bacteria, Eubacteria, Microorganisms

L6 ANSWER 2 OF 12 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
DUPLICATE 2

AN 2006:614816 BIOSIS <<LOGINID::20080330>>

DN PREV200600621274

TI Mycobacterium ***tuberculosis*** Delta RD1 Delta panCD: A safe and limited replicating mutant strain that protects immunocompetent and immunocompromised mice against experimental ***tuberculosis*** .

AU ***Sambandamurthy, Vasan K.*** [Reprint Author]; Derrick, Steven C.; Hsu, Tsungda; Chen, Bing; Larsen, Michelle H.; Jalapathy, Kripa V.; Chen, Mei; Kim, John; Porcelli, Steven A.; Chan, John; Morris, Sheldon L.; Jacobs, William R. Jr.

CS US FDA, Ctr Biol Evaluat and Res, Bethesda, MD 20892 USA
jacobsw@hhmi.org

SO Vaccine, (SEP 11 2006) Vol. 24, No. 37-39, pp. 6309-6320.

CODEN: VACCDE. ISSN: 0264-410X.
DT Article
LA English
ED Entered STN: 15 Nov 2006
Last Updated on STN: 15 Nov 2006
AB The global epidemic of ***tuberculosis*** (TB), fueled by the growing HIV pandemic, warrants the development of a safe and effective vaccine against TB. We report the construction and characterization of an unlinked double deletion mutant of Mycobacterium ***tuberculosis*** H37Rv that deletes both the primary attenuating mutation of BCG (Delta RD1) and two genes required for the synthesis of pantothenate (Delta panCD). The M. ***tuberculosis*** Delta RD1 Delta panCD (mc(2)6030) mutant undergoes limited replication in mice, and yet is both significantly safer than BCG in immunocompromised mice and also safe in guinea pigs. Additionally, the mc(2)6030 strain does not reactivate in a mouse chemo-immunosuppression model. Importantly, long-lived protective immune responses following immunization with the mc(2)6030 strain prolong the survival of wild type mice, and CD4-deficient mice against an aerosol challenge with virulent M. ***tuberculosis*** . Given its overall safety and effectiveness, the mc(2)6030 live attenuated strain should be considered as a human vaccine candidate for protecting both healthy and HIV-infected individuals against TB.
TI Mycobacterium ***tuberculosis*** Delta RD1 Delta panCD: A safe and limited replicating mutant strain that protects immunocompetent and immunocompromised mice against experimental ***tuberculosis*** .
AU ***Sambandamurthy, Vasan K.*** [Reprint Author]; Derrick, Steven C.; Hsu, Tsungda; Chen, Bing; Larsen, Michelle H.; Jalapathy, Kripa V.; Chen, Mei; Kim,. . .
AB The global epidemic of ***tuberculosis*** (TB), fueled by the growing HIV pandemic, warrants the development of a safe and effective vaccine against TB. We report the construction and characterization of an unlinked double deletion mutant of Mycobacterium ***tuberculosis*** H37Rv that deletes both the primary attenuating mutation of BCG (Delta RD1) and two genes required for the synthesis of pantothenate (Delta panCD). The M. ***tuberculosis*** Delta RD1 Delta panCD (mc(2)6030) mutant undergoes limited replication in mice, and yet is both significantly safer than BCG in. . . the mc(2)6030 strain prolong the survival of wild type mice, and CD4-deficient mice against an aerosol challenge with virulent M. ***tuberculosis*** . Given its overall safety and effectiveness, the mc(2)6030 live attenuated strain should be considered as a human vaccine candidate for. . .
IT Major Concepts
Pharmacology; Infection; Immune System (Chemical Coordination and Homeostasis)
IT Diseases
experimental ***tuberculosis*** : bacterial disease, infectious disease, prevention and control
IT Chemicals & Biochemicals
CD4; ***tuberculosis*** vaccine: immunologic-drug, immunostimulant-drug
ORGN . . .
Mammals, Rodents, Vertebrates
ORGN Classifier
Mycobacteriaceae 08881
Super Taxa
Mycobacteria; Actinomycetes and Related Organisms; Eubacteria;

Bacteria; Microorganisms
Organism Name
Mycobacterium ***tuberculosis*** (species): pathogen, strain-H37Rv, strain-delta-RD1, strain-delta-panCD, strain-mc-2-6030, strain-BCG Pasteur, strain-Erdman
Taxa Notes
Bacteria, Eubacteria, Microorganisms
ORGN Classifier
Retroviridae 03305
Super Taxa

L6 ANSWER 3 OF 12 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
DUPLICATE 3
AN 2006:285376 BIOSIS <<LOGINID::20080330>>
DN PREV200600284461
TI Induction of high levels of protective immunity in mice after vaccination using dendritic cells infected with auxotrophic mutants of Mycobacterium ***tuberculosis*** .
AU Roy, Eleanor; De Silva, A. Dharshan; ***Sambandamurthy, Vasan K.*** ; Clark, Simon O.; Stavropoulos, Evangelos; Jacobs, William R. Jr; Brennan, John; Chan, John; Williams, Ann; Colston, M. Joseph; Tascon, Ricardo E. [Reprint Author]
CS Natl Inst Med Res, Mycobacterial Div, Mill Hill, London NW7 1AA, UK
tricard@nimr.mrc.ac.uk
SO Immunology Letters, (MAR 15 2006) Vol. 103, No. 2, pp. 196-199.
CODEN: IMLED6. ISSN: 0165-2478.
DT Article
LA English
ED Entered STN: 24 May 2006
Last Updated on STN: 24 May 2006
AB Adoptively transferred dendritic cells presenting antigens derived from different pathogens have been shown to elicit specific T cell responses and to induce protective antibacterial immunity. We describe here the induction of high levels of protective immunity in mice using dendritic cells infected with auxotrophic mutants of Mycobacterium ***tuberculosis*** . We provide evidence that protection is superior to BCG and that it is associated with increased priming of CD4(+) and CD8(+) T cells specific for mycobacterial antigens. This method for generating high levels of anti-bacterial protective immunity could be helpful in the design of novel vaccines against ***tuberculosis*** and other intracellular pathogens. (C) 2005 Elsevier B.V. All rights reserved.
TI. . . Induction of high levels of protective immunity in mice after vaccination using dendritic cells infected with auxotrophic mutants of Mycobacterium ***tuberculosis*** .
AU Roy, Eleanor; De Silva, A. Dharshan; ***Sambandamurthy, Vasan K.*** ; Clark, Simon O.; Stavropoulos, Evangelos; Jacobs, William R. Jr; Brennan, John; Chan, John; Williams, Ann; Colston, M. Joseph;. . .
AB. . . here the induction of high levels of protective immunity in mice using dendritic cells infected with auxotrophic mutants of Mycobacterium ***tuberculosis*** . We provide evidence that protection is superior to BCG and that it is associated with increased priming of CD4(+) and. . . This method for generating high levels of anti-bacterial protective immunity could be helpful in the design of novel vaccines against ***tuberculosis*** and other intracellular pathogens. (C) 2005 Elsevier B.V. All rights reserved.
ORGN . . .
Mammals, Rodents, Vertebrates

ORGN Classifier
Mycobacteriaceae 08881
Super Taxa
Mycobacteria; Actinomycetes and Related Organisms; Eubacteria; Bacteria; Microorganisms
Organism Name
Mycobacterium ***tuberculosis*** (species): pathogen, auxotrophic mutant
Taxa Notes
Bacteria, Eubacteria, Microorganisms

L6 ANSWER 4 OF 12 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2005:1242628 CAPLUS <<LOGINID::20080330>>
DN 144:5382
TI RD1 region-altered or deleted Mycobacterium ***tuberculosis*** as vaccines for treating ***tuberculosis*** in mammal and human
IN Jacobs, William R., Jr.; Bloom, Barry; Hondalus, Mary K.; Sampson, Samantha; ***Sambandamurthy, Vasan***
PA USA
SO U.S. Pat. Appl. Publ., 76 pp., Cont.-in-part of U.S. Ser. No. 351,452.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2005260232	A1	20051124	US 2005-109056	20050419
	US 2004001866	A1	20040101	US 2003-351452	20030124
PRAI	US 2002-358152P	P	20020219		
	US 2003-351452	A2	20030124		

AB Non-naturally occurring mycobacteria in the Mycobacterium ***tuberculosis*** complex are provided. These mycobacteria have a deletion of an RD1 region or a region (e.g. leuD or panCD genes) controlling prodn. of a vitamin, and exhibit attenuated virulence in a mammal when compared to the mycobacteria without the deletion. Also provided are non-naturally occurring mycobacteria that have a deletion of a region controlling prodn. of lysine, and mycobacteria comprising two attenuating deletions. Vaccines comprising these mycobacteria are also provided, as are methods of protecting mammals from virulent mycobacteria using the vaccines. Also provided are methods of prepg. these vaccines which include the step of deleting an RD1 region or a region controlling prodn. of a vitamin or the amino acids leucine and lysine from a mycobacterium in the M. ***tuberculosis*** complex. Embodiments of these mycobacteria, vaccines and methods, encompassing mycobacteria comprising a leucine auxotrophy and a pantothenate auxotrophy, are also provided.

TI RD1 region-altered or deleted Mycobacterium ***tuberculosis*** as vaccines for treating ***tuberculosis*** in mammal and human
IN Jacobs, William R., Jr.; Bloom, Barry; Hondalus, Mary K.; Sampson, Samantha; ***Sambandamurthy, Vasan***
AB Non-naturally occurring mycobacteria in the Mycobacterium ***tuberculosis*** complex are provided. These mycobacteria have a deletion of an RD1 region or a region (e.g. leuD or panCD genes). . . a region controlling prodn. of a vitamin or the amino acids leucine and lysine from a mycobacterium in the M. ***tuberculosis*** complex. Embodiments of these mycobacteria, vaccines and methods, encompassing mycobacteria comprising a leucine auxotrophy and a pantothenate

auxotrophy, are also. . .
ST RD1 leuD panCD gene deletion mutation Mycobacterium ***tuberculosis*** vaccine; leucine lysine pantothenate vitamin auxotrophy Mycobacterium ***tuberculosis*** complex vaccine
IT Mycobacterium ***tuberculosis***
(H37Rv; RD1 region-altered or deleted Mycobacterium ***tuberculosis*** as vaccines for treating ***tuberculosis*** in
mammal and human)
IT Bos taurus
DNA sequences
Drug delivery systems
Human
Mammalia
Molecular cloning
Mutagenesis
Mycobacterium bovis
Tuberculosis
Vaccines
(RD1 region-altered or deleted Mycobacterium ***tuberculosis*** as vaccines for treating ***tuberculosis*** in mammal and human)
IT Vitamins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(RD1 region-altered or deleted Mycobacterium ***tuberculosis*** as vaccines for treating ***tuberculosis*** in mammal and human)
IT Gene, microbial
RL: BSU (Biological study, unclassified); PRP (Properties); REM (Removal or disposal); BIOL (Biological study); PROC (Process)
(RD1; RD1 region-altered or deleted Mycobacterium ***tuberculosis*** as vaccines for treating ***tuberculosis*** in mammal and human)
IT Microorganism
(auxotrophic; leucine/lysine/pantothenate-auxotrophic Mycobacterium ***tuberculosis*** as vaccines for treating ***tuberculosis*** in
mammal and human)
IT Gene, microbial
RL: BSU (Biological study, unclassified); PRP (Properties); REM (Removal or disposal); BIOL (Biological study); PROC (Process)
(leuD; RD1 region-altered or deleted Mycobacterium ***tuberculosis*** as vaccines for treating ***tuberculosis*** in mammal and human)
IT Gene, microbial
RL: BSU (Biological study, unclassified); PRP (Properties); REM (Removal or disposal); BIOL (Biological study); PROC (Process)
(lysA; RD1 region-altered or deleted Mycobacterium ***tuberculosis*** as vaccines for treating ***tuberculosis*** in mammal and human)
IT Gene, microbial
RL: BSU (Biological study, unclassified); PRP (Properties); REM (Removal or disposal); BIOL (Biological study); PROC (Process)
(nadBC; RD1 region-altered or deleted Mycobacterium ***tuberculosis*** as vaccines for treating ***tuberculosis*** in
mammal and human)
IT Gene, microbial
RL: BSU (Biological study, unclassified); PRP (Properties); REM (Removal or disposal); BIOL (Biological study); PROC (Process)
(panCD; RD1 region-altered or deleted Mycobacterium

tuberculosis as vaccines for treating ***tuberculosis*** in
mammal and human)
IT Mutagenesis
(site-directed, deletion; RD1 region-altered or deleted Mycobacterium
tuberculosis as vaccines for treating ***tuberculosis*** in
mammal and human)
IT 56-87-1, L-Lysine, biological studies 61-90-5, L-Leucine, biological studies 79-83-4
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(RD1 region-altered or deleted Mycobacterium ***tuberculosis*** as vaccines for treating ***tuberculosis*** in mammal and human)
IT 870107-04-3 870107-05-4 870107-06-5 870107-07-6 870107-08-7
RL: BSU (Biological study, unclassified); PRP (Properties); REM (Removal or disposal); BIOL (Biological study); PROC (Process)
(nucleotide sequence; RD1 region-altered or deleted Mycobacterium
tuberculosis as vaccines for treating ***tuberculosis*** in
mammal and human)
IT 870109-36-7 870109-37-8 870109-38-9 870109-39-0 870109-40-3 870109-41-4 870109-42-5
RL: PRP (Properties)
(unclaimed nucleotide sequence; rD1 region-altered or deleted Mycobacterium ***tuberculosis*** as vaccines for treating
tuberculosis in mammal and human)

L6 ANSWER 5 OF 12 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
DUPLICATE 4
AN 2005:169360 BIOSIS <<LOGINID::20080330>>
DN PREV200500170314
TI Long-term protection against ***tuberculosis*** following vaccination with a severely attenuated double lysine and pantothenate auxotroph of Mycobacterium ***tuberculosis*** .
AU ***Sambandamurthy, Vasan K.*** ; Derrick, Steven C.; Jalapathy, Kripa V.; Chen, Bing; Russell, Robert G.; Morris, Sheldon L.; Jacobs, William R. Jr [Reprint Author]
CS Howard Hughes Med Inst, Albert Einstein Coll Med, 1300 Morris Pk Ave, Bronx, NY, 10461, USA
jacobsw@hhmi.org
SO Infection and Immunity, (February 2005) Vol. 73, No. 2, pp. 1196-1203. print.
ISSN: 0019-9567 (ISSN print).
DT Article
LA English
ED Entered STN: 4 May 2005
Last Updated on STN: 4 May 2005
AB We report the safety and immunogenicity of a double lysine and pantothenate auxotroph of Mycobacterium ***tuberculosis*** in mice. The DELTAlysDELTA DELTApanCD mutant is completely attenuated in immunocompromised SCID and gamma interferon knockout mice yet induces short-term and long-term protection in immunocompetent and CD4-deficient mice following single-dose subcutaneous vaccination.
TI Long-term protection against ***tuberculosis*** following vaccination with a severely attenuated double lysine and pantothenate auxotroph of Mycobacterium ***tuberculosis*** .
AU ***Sambandamurthy, Vasan K.*** ; Derrick, Steven C.; Jalapathy, Kripa

V.; Chen, Bing; Russell, Robert G.; Morris, Sheldon L.; Jacobs, William R. Jr. . .

AB We report the safety and immunogenicity of a double lysine and pantothenate auxotroph of Mycobacterium ***tuberculosis*** in mice. The DELTAlysDELTA DELTApanCD mutant is completely attenuated in immunocompromised SCID and gamma interferon knockout mice yet induces short-term. . .

IT Major Concepts
Immune System (Chemical Coordination and Homeostasis); Infection; Pharmacology

IT Diseases
tuberculosis : bacterial disease, drug therapy
Tuberculosis (MeSH)

IT Chemicals & Biochemicals
lysine-pantothenate double auxotroph vaccine: immunologic-drug, immunostimulant-drug, subcutaneous administration

ORGN . . .
Mammals, Rodents, Vertebrates

ORGN Classifier
Mycobacteriaceae 08881

Super Taxa
Mycobacteria; Actinomycetes and Related Organisms; Eubacteria; Bacteria; Microorganisms

Organism Name
Mycobacterium ***tuberculosis*** (species): pathogen, strain-BCG-P, strain-H37Rv, strain-MC-26020

Taxa Notes
Bacteria, Eubacteria, Microorganisms

L6 ANSWER 6 OF 12 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN DUPLICATE 5

AN 2005:392197 BIOSIS <<LOGINID::20080330>>

DN PREV200510180290

TI Live attenuated mutants of Mycobacterium ***tuberculosis*** as candidate vaccines against ***tuberculosis*** .

AU ***Sambandamurthy, Vasan K.*** ; Jacobs, William R. Jr [Reprint Author]

CS Yeshiva Univ Albert Einstein Coll Med, Howard Hughes Med Inst, Dept Microbiol and Immunol, 1300 Morris Pk Ave, Bronx, NY 10461 USA
jacobsw@hhmi.org

SO Microbes and Infection, (MAY 2005) Vol. 7, No. 5-6, pp. 955-961.
ISSN: 1286-4579.

DT Article

LA English

ED Entered STN: 28 Sep 2005
Last Updated on STN: 28 Sep 2005

AB The recent advances in genetic tools to manipulate Mycobacterium ***tuberculosis*** have led to the construction of defined mutants and to the study of their role in the virulence and pathogenesis of ***tuberculosis*** . The safety and vaccine potential of a few of these M. ***tuberculosis*** mutants as candidate vaccines against ***tuberculosis*** are discussed. (c) 2005 Elsevier SAS. All rights reserved.

TI Live attenuated mutants of Mycobacterium ***tuberculosis*** as candidate vaccines against ***tuberculosis*** .

AU ***Sambandamurthy, Vasan K.*** ; Jacobs, William R. Jr [Reprint Author]

AB The recent advances in genetic tools to manipulate Mycobacterium ***tuberculosis*** have led to the construction of defined mutants and

to the study of their role in the virulence and pathogenesis of ***tuberculosis*** . The safety and vaccine potential of a few of these M. ***tuberculosis*** mutants as candidate vaccines against ***tuberculosis*** are discussed. (c) 2005 Elsevier SAS. All rights reserved.

IT Major Concepts
Pharmacology; Infection

IT Diseases
tuberculosis : bacterial disease, etiology
Tuberculosis (MeSH)

IT Chemicals & Biochemicals
candidate vaccine: antiinfective-drug

ORGN Classifier
Mycobacteriaceae 08881

Super Taxa
Mycobacteria; Actinomycetes and Related Organisms; Eubacteria; Bacteria; Microorganisms

Organism Name
Mycobacterium ***tuberculosis*** (species): pathogen, attenuated mutant

Taxa Notes
Bacteria, Eubacteria, Microorganisms

L6 ANSWER 7 OF 12 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2004:648328 CAPLUS <<LOGINID::20080330>>
DN 141:172863
TI Mycobacterial vaccine comprising deletion mutagenesis in RD1 region, and vitamin and amino acid production-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes
IN Bardarov, Stoyan; Jacobs, William R., Jr.; Hsu, Tsungda; ***Sambandamurthy, Vasan*** ; Morris, Sheldon
PA Albert Einstein College of Medicine of Yeshiva University, USA
SO PCT Int. Appl., 116 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004066928	A2	20040812	WO 2004-US1773	20040123
	WO 2004066928	A3	20060105		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	US 2007202131	A1	20070830	US 2007-542958	20070130
PRAI	US 2003-442631P	P	20030124		
	WO 2004-US1773	W	20040123		

AB Methods of treating a mammal that is deficient in CD4+ and/or CD8+ lymphocytes are provided. The methods comprise inoculating the mammal with an attenuated mycobacterium in the M. ***tuberculosis*** complex.

In these methods, the mycobacterium comprises two deletions, wherein a virulent mycobacterium in the M. ***tuberculosis*** complex having either deletion exhibits attenuated virulence. The two deletions is a deletion of RD1 region, region controlling prodn. of vitamin (e.g. pantothenic acid or NAD), and region controlling prodn. of amino acid (e.g. proline, tryptophan, leucine, or lysin). The deletion is .DELTA.panCD deletion and .DELTA.lysA deletion. Use of these mycobacteria for the manuf. of a medicament for the treatment of mammals deficient in CD4+ and/or CD8+ lymphocytes is also provided.

IN Bardarov, Stoyan; Jacobs, William R., Jr.; Hsu, Tsungda; ***Sambandamurthy, Vasan*** ; Morris, Sheldon

AB . . . in CD4+ and/or CD8+ lymphocytes are provided. The methods comprise inoculating the mammal with an attenuated mycobacterium in the M. ***tuberculosis*** complex. In these methods, the mycobacterium comprises two deletions, wherein a virulent mycobacterium in the M. ***tuberculosis*** complex having either deletion exhibits attenuated virulence. The two deletions is a deletion of RD1 region, region controlling prodn. of. . .

ST Mycobacterium ***tuberculosis*** complex deletion RD1 vitamin amino acid prodn; mycobacterial vaccine RD1 panCD lysA deletion CD4 CD8 lymphocyte

IT Mycobacterium ***tuberculosis***
(H37Rv and CDC1551 strains; mycobacterial vaccine comprising deletion mutagenesis in RD1 region, and vitamin and amino acid prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

IT Borrelia
Bos taurus
CD4-positive T cell
CD8-positive T cell
DNA sequences
Genetic engineering
Herpesviridae
Human
Human herpesvirus
Human immunodeficiency virus
Human poliovirus
Immunostimulants
Leishmania
Mammalia
Measles virus
Molecular cloning
Mumps virus
Mycobacterium
Mycobacterium africanum
Mycobacterium avium
Mycobacterium bovis
Mycobacterium intracellulare
Mycobacterium leprae
Neisseria
Pertussis
Rabies virus
Salmonella
Shigella
Transduction, genetic
Treponema
Tuberculosis

Vibrio cholerae
(mycobacterial vaccine comprising deletion mutagenesis in RD1 region, and vitamin and amino acid prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

L6 ANSWER 8 OF 12 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
DUPLICATE 6
AN 2004:338315 BIOSIS <<LOGINID::20080330>>
DN PREV200400338496
TI Protection elicited by a double leucine and pantothenate auxotroph of Mycobacterium ***tuberculosis*** in guinea pigs.
AU Sampson, Samantha L.; Dascher, Christopher C.; ***Sambandamurthy, Vasan***
*** K.*** ; Russell, Robert G.; Jacobs, William R. Jr; Bloom, Barry R.; Hondalus, Mary K. [Reprint Author]
CS Sch Publ HlthDept Immunol and Infect Dis, Harvard Univ, 665 Huntington Ave, Boston, MA, 02115, USA
mhondalu@hsph.harvard.edu
SO Infection and Immunity, (May 2004) Vol. 72, No. 5, pp. 3031-3037. print.
ISSN: 0019-9567 (ISSN print).
DT Article
LA English
ED Entered STN: 11 Aug 2004
Last Updated on STN: 11 Aug 2004
AB We developed a live, fully attenuated Mycobacterium ***tuberculosis*** vaccine candidate strain with two independent attenuating auxotrophic mutations in leucine and pantothenate biosynthesis. The DELTAleuD DELTApanCD double auxotroph is fully attenuated in the SCID mouse model and highly immunogenic and protective in the extremely sensitive guinea pig ***tuberculosis*** model, reducing both bacterial burden and disease pathology.
TI Protection elicited by a double leucine and pantothenate auxotroph of Mycobacterium ***tuberculosis*** in guinea pigs.
AU Sampson, Samantha L.; Dascher, Christopher C.; ***Sambandamurthy, Vasan***
*** K.*** ; Russell, Robert G.; Jacobs, William R. Jr; Bloom, Barry R.; Hondalus, Mary K. [Reprint Author]
AB We developed a live, fully attenuated Mycobacterium ***tuberculosis*** vaccine candidate strain with two independent attenuating auxotrophic mutations in leucine and pantothenate biosynthesis. The DELTAleuD DELTApanCD double auxotroph is fully attenuated in the SCID mouse model and highly immunogenic and protective in the extremely sensitive guinea pig ***tuberculosis*** model, reducing both bacterial burden and disease pathology.
IT . . . Concepts
Immune System (Chemical Coordination and Homeostasis); Infection; Molecular Genetics (Biochemistry and Molecular Biophysics); Respiratory System (Respiration)
IT Diseases
pulmonary ***tuberculosis*** : bacterial disease, respiratory system disease, therapy
Tuberculosis , Pulmonary (MeSH)
ORGN . . .
Mammals, Rodents, Vertebrates
ORGN Classifier
Mycobacteriaceae 08881
Super Taxa

Mycobacteria; Actinomycetes and Related Organisms; Eubacteria; Bacteria; Microorganisms

Organism Name

Mycobacterium ***tuberculosis*** (species): pathogen, double leucine mutant auxotroph, guinea pig vaccination, lung infection protection, pantothenate mutant auxotroph, severe combined immunodeficiency mouse attenuation

L6 ANSWER 9 OF 12 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2003:678598 CAPLUS <<LOGINID::20080330>>
DN 139:212868
TI Attenuated Mycobacterium ***tuberculosis*** vaccines comprising deletion of RD1 region
IN Jacobs, William R., Jr.; Hsu, Tsungda; Bardarov, Stoyan; ***Sambandamurthy, Vasan***
PA Albert Einstein College of Medicine of Yeshiva University, USA
SO PCT Int. Appl., 102 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003070164	A2	20030828	WO 2003-US2046	20030124
	WO 2003070164	A3	20060216		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	AU 2003209345	A1	20030909	AU 2003-209345	20030124
PRAI	US 2002-358152P	P	20020219		
	WO 2003-US2046	W	20030124		

AB Non-naturally occurring mycobacteria in the Mycobacterium ***tuberculosis*** complex are provided. These mycobacteria have a deletion of an RD1 region or a region controlling prodn. of a vitamin, and exhibit attenuated virulence in a mammal when compared to the mycobacteria without the deletion. Also provided are non-naturally occurring mycobacteria that have a deletion of a region controlling prodn. of lysine, and mycobacteria comprising two attenuating deletions. Vaccines comprising these mycobacteria are also provided, as are methods of protecting mammals from virulent mycobacteria using the vaccines. Also provided are methods of prepg. these vaccines which include the step of deleting an RD1 region or a region controlling prodn. of a vitamin from a mycobacterium in the M ***tuberculosis*** complex.

TI Attenuated Mycobacterium ***tuberculosis*** vaccines comprising deletion of RD1 region
IN Jacobs, William R., Jr.; Hsu, Tsungda; Bardarov, Stoyan; ***Sambandamurthy, Vasan***
AB Non-naturally occurring mycobacteria in the Mycobacterium ***tuberculosis*** complex are provided. These mycobacteria have a deletion of an RD1 region or a region controlling prodn. of a vitamin,. .

. step of deleting an RD1 region or a region controlling prodn. of a vitamin from a mycobacterium in the M ***tuberculosis*** complex.

ST Mycobacterium ***tuberculosis*** vitamin pantothenic acid NAD RD1 region deletion; antigen vaccine Mycobacterium ***tuberculosis*** RD1 deletion

IT Borrelia
Bos taurus
DNA sequences
Genetic engineering
Genetic markers
Herpesviridae
Human
Human immunodeficiency virus
Human poliovirus
Immunodeficiency
Immunostimulants
Infection
Leishmania
Mammalia
Measles virus
Molecular cloning
Mumps virus
Mus
Mycobacterium BCG
Mycobacterium africanum
Mycobacterium avium
Mycobacterium bovis
Mycobacterium intracellulare
Mycobacterium leprae
Mycobacterium ***tuberculosis***
Neisseria
Pertussis
Rabies
Recombination, genetic
Salmonella
Shigella
Transduction, genetic
Treponema
Vaccines
Vibrio cholerae
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Vitamins
RL: BSU (Biological study, unclassified); REM (Removal or disposal); BIOL (Biological study); PROC (Process)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Antigens
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Enzymes, biological studies
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Interleukin 1
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)
IT Interleukin 2
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)
IT Interleukin 3
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)
IT Interleukin 4
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)
IT Interleukin 5
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)
IT Interleukin 6
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)
IT Interleukin 7
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)
IT Lymphokines
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)
IT Lymphotoxin
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)
IT Reporter gene
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)
IT Tumor necrosis factors
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)
IT Microorganism
(auxotrophic; attenuated Mycobacterium ***tuberculosis***

comprising deletion of RD1 region for vaccine prepns.)
IT Development, mammalian postnatal
(child; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)
IT Toxoids
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(diphtheria; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)
IT Steroids, biological studies
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(enzyme; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)
IT Drug delivery systems
(injections, s.c.; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)
IT Venoms
(insect; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)
IT Drug delivery systems
(intradermal; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)
IT Development, microbial
(merozoite, malaria; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)
IT DNA
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(recombinant; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)
IT Gene, microbial
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(sacB; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)
IT Mutagenesis
(site-directed, deletion; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)
IT Venoms
(snake; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)
IT Development, microbial
(sporozoite, malaria; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)
IT Toxoids
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tetanus; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)
IT ***Tuberculosis***
(vaccine; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)
IT Insecta
(venom; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)
IT Interferons

RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.alpha.; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Interferons
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.beta.; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Interferons
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.gamma.; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT 53-84-9, Nicotinamide adenine dinucleotide 56-87-1, L-Lysine, biological studies 61-90-5, L-Leucine, biological studies 73-22-3, L-Tryptophan, biological studies 79-83-4, Pantothenic acid 147-85-3, L-Proline, biological studies
RL: BSU (Biological study, unclassified); REM (Removal or disposal); BIOL (Biological study); PROC (Process)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT 9001-45-0, .beta. Glucuronidase 9014-00-0, Luciferase 9031-11-2, .beta. Galactosidase 63774-46-9
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT 588746-25-2P
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(nucleotide sequence; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT 588746-26-3 588746-27-4 588746-28-5
RL: BSU (Biological study, unclassified); PRP (Properties); REM (Removal or disposal); BIOL (Biological study); PROC (Process)
(nucleotide sequence; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT 588747-89-1 588747-90-4 588747-91-5 588747-92-6 588747-93-7 588747-94-8 588747-95-9 588747-96-0
RL: PRP (Properties)
(unclaimed nucleotide sequence; attenuated Mycobacterium ***tuberculosis*** vaccines comprising deletion of RD1 region)

L6 ANSWER 10 OF 12 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN DUPLICATE 7

AN 2003:575250 BIOSIS <<LOGINID::20080330>>

DN PREV200300578624

TI Survival perspectives from the world's most successful pathogen, Mycobacterium ***tuberculosis*** .

AU Hingley-Wilson, Suzanne M.; ***Sambandamurthy, Vasan K.*** ; Jacobs, William R. Jr. [Reprint Author]

CS Howard Hughes Medical Institute, Albert Einstein College of Medicine, Bronx, NY, 10461, USA
jacobsw@hhmi.org

SO Nature Immunology, (October 2003) Vol. 4, No. 10, pp. 949-955. print.

ISSN: 1529-2908 (ISSN print).
DT Article
General Review; (Literature Review)
LA English
ED Entered STN: 10 Dec 2003
Last Updated on STN: 10 Dec 2003
AB Studying defined mutants of Mycobacterium ***tuberculosis*** in the mouse model of infection has led to the discovery of attenuated mutants that fall into several phenotypic classes. These mutants are categorized by their growth characteristics compared with those of wild-type M. ***tuberculosis*** , and include severe growth in vivo mutants, growth in vivo mutants, persistence mutants, pathology mutants and dissemination mutants. Here, examples of each of these mutant phenotypes are described and classified accordingly. Defining the importance of mycobacterial gene products responsible for in vivo growth, persistence and the induction of immunopathology will lead to a greater understanding of the host-pathogen interaction and potentially to new antimycobacterial treatment options.
TI Survival perspectives from the world's most successful pathogen, Mycobacterium ***tuberculosis*** .
AU Hingley-Wilson, Suzanne M.; ***Sambandamurthy, Vasan K.*** ; Jacobs, William R. Jr. [Reprint Author]
AB Studying defined mutants of Mycobacterium ***tuberculosis*** in the mouse model of infection has led to the discovery of attenuated mutants that fall into several phenotypic classes. These mutants are categorized by their growth characteristics compared with those of wild-type M. ***tuberculosis*** , and include severe growth in vivo mutants, growth in vivo mutants, persistence mutants, pathology mutants and dissemination mutants. Here, examples. . .
ORGN . . .
Mammals, Rodents, Vertebrates
ORGN Classifier
Mycobacteriaceae 08881
Super Taxa
Mycobacteria; Actinomycetes and Related Organisms; Eubacteria; Bacteria; Microorganisms
Organism Name
Mycobacterium ***tuberculosis*** (species): pathogen, attenuated mutants, dissemination mutants, in vivo mutants, pathology mutants, persistence mutants, severe growth
Taxa Notes
Bacteria, Eubacteria, Microorganisms

L6 ANSWER 11 OF 12 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN DUPLICATE 8
AN 2002:600487 BIOSIS <<LOGINID::20080330>>
DN PREV200200600487
TI Specialized transduction: An efficient method for generating marked and unmarked targeted gene disruptions in Mycobacterium ***tuberculosis*** , M. bovis BCG and M. smegmatis.
AU Bardarov, Stoyan; Bardarov, Svetoslav; Pavelka, Martin S., Jr.; ***Sambandamurthy, Vasan*** ; Larsen, Michelle; Tufariello, JoAnn; Chan, John; Hatfull, Graham; Jacobs, William R., Jr. [Reprint author]
CS Dept of Microbiology and Immunology, Howard Hughes Medical Institute, Albert Einstein College of Medicine, Bronx, NY, 10461, USA
jacobsw@hhmi.org

SO Microbiology (Reading), (October, 2002) Vol. 148, No. 10, pp. 3007-3017. print.
ISSN: 1350-0872.
DT Article
LA English
ED Entered STN: 20 Nov 2002
Last Updated on STN: 20 Nov 2002
AB The authors have developed a simple and highly efficient system for generating allelic exchanges in both fast- and slow-growing mycobacteria. In this procedure a gene of interest, disrupted by a selectable marker, is cloned into a conditionally replicating (temperature-sensitive) shuttle phasmid to generate a specialized transducing mycobacteriophage. The temperature-sensitive mutations in the mycobacteriophage genome permit replication at the permissive temperature of 30degreeC but prevent replication at the non-permissive temperature of 37degreeC. Transduction at a non-permissive temperature results in highly efficient delivery of the recombination substrate to virtually all cells in the recipient population. The deletion mutations in the targeted genes are marked with antibiotic-resistance genes that are flanked by gammadelta-res (resolvase recognition target) sites. The transductants which have undergone a homologous recombination event can be conveniently selected on antibiotic-containing media. To demonstrate the utility of this genetic system seven different targeted gene disruptions were generated in three substrains of Mycobacterium bovis BCG, three strains of Mycobacterium ***tuberculosis*** , and Mycobacterium smegmatis. Mutants in the lysA, nadBC, panC, panCD, leuCD, Rv3291c and Rv0867c genes or operons were isolated as antibiotic-resistant (and in some cases auxotrophic) transductants. Using a plasmid encoding the gammadelta-resolvase (tnpR), the resistance genes could be removed, generating unmarked deletion mutations. It is concluded from the high frequency of allelic exchange events observed in this study that specialized transduction is a very efficient technique for genetic manipulation of mycobacteria and is a method of choice for constructing isogenic strains of M. ***tuberculosis*** , BCG or M. smegmatis which differ by defined mutations.
TI Specialized transduction: An efficient method for generating marked and unmarked targeted gene disruptions in Mycobacterium ***tuberculosis*** , M. bovis BCG and M. smegmatis.
AU Bardarov, Stoyan; Bardarov, Svetoslav; Pavelka, Martin S., Jr.; ***Sambandamurthy, Vasan*** ; Larsen, Michelle; Tufariello, JoAnn; Chan, John; Hatfull, Graham; Jacobs, William R., Jr. [Reprint author]
AB. . . genetic system seven different targeted gene disruptions were generated in three substrains of Mycobacterium bovis BCG, three strains of Mycobacterium ***tuberculosis*** , and Mycobacterium smegmatis. Mutants in the lysA, nadBC, panC, panCD, leuCD, Rv3291c and Rv0867c genes or operons were isolated as. . . very efficient technique for genetic manipulation of mycobacteria and is a method of choice for constructing isogenic strains of M. ***tuberculosis*** , BCG or M. smegmatis which differ by defined mutations.
IT Major Concepts
Epidemiology (Population Studies); Infection; Molecular Genetics (Biochemistry and Molecular Biophysics); Pharmacology
IT Diseases
tuberculosis : bacterial disease
Tuberculosis (MeSH)
ORGN . . .
08881

Super Taxa
Mycobacteria; Actinomycetes and Related Organisms; Eubacteria; Bacteria; Microorganisms
Organism Name
Mycobacterium bovis BCG: pathogen
Mycobacterium bovis smegmatis: pathogen
Mycobacterium ***tuberculosis*** : pathogen
Taxa Notes
Bacteria, Eubacteria, Microorganisms

L6 ANSWER 12 OF 12 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN DUPLICATE 9
AN 2002:542024 BIOSIS <<LOGINID::20080330>>
DN PREV200200542024
TI A pantothenate auxotroph of Mycobacterium ***tuberculosis*** is highly attenuated and protects mice against ***tuberculosis*** .
AU ***Sambandamurthy, Vasan K.*** ; Wang, Xiaojuan; Chen, Bing; Russell, Robert G.; Derrick, Steven; Collins, Frank M.; Morris, Sheldon L.; Jacobs, William R., Jr. [Reprint author]
CS Department of Microbiology and Immunology, Howard Hughes Medical Institute, Bronx, NY, USA
jacobsw@hhmi.org
SO Nature Medicine, (October, 2002) Vol. 8, No. 10, pp. 1171-1174. print.
ISSN: 1078-8956.
DT Article
LA English
ED Entered STN: 23 Oct 2002
Last Updated on STN: 23 Oct 2002
AB With the advent of HIV and the widespread emergence of drug-resistant strains of Mycobacterium ***tuberculosis*** , newer control strategies in the form of a better vaccine could decrease the global incidence of ***tuberculosis*** . A desirable trait in an effective live attenuated vaccine strain is an ability to persist within the host in a limited fashion in order to produce important protective antigens in vivo. Attenuated M. ***tuberculosis*** vaccine candidates have been constructed by deleting genes required for growth in mice. These candidate vaccines did not elicit adequate protective immunity in animal models, due to their inability to persist sufficiently long within the host tissues. Here we report that an auxotrophic mutant of M. ***tuberculosis*** defective in the de novo biosynthesis of pantothenic acid (vitamin B5) is highly attenuated in immunocompromised SCID mice and in immunocompetent BALB/c mice. SCID mice infected with the pantothenate auxotroph survived significantly longer (250 days) than mice infected with either bacille Calmette-Guerin (BCG) vaccine or virulent M. ***tuberculosis*** (77 and 35 days, respectively). Subcutaneous immunization with this auxotroph conferred protection in C57BL/6J mice against an aerosol challenge with virulent M. ***tuberculosis*** , which was comparable with that afforded by BCG vaccination. Our findings highlight the importance of de novo pantothenate biosynthesis in limiting the intracellular survival and pathogenesis of M. ***tuberculosis*** without reducing its immunogenicity in vaccinated mice.
TI A pantothenate auxotroph of Mycobacterium ***tuberculosis*** is highly attenuated and protects mice against ***tuberculosis*** .
AU ***Sambandamurthy, Vasan K.*** ; Wang, Xiaojuan; Chen, Bing; Russell, Robert G.; Derrick, Steven; Collins, Frank M.; Morris, Sheldon L.; Jacobs, William R.,. . .
AB With the advent of HIV and the widespread emergence of drug-resistant

strains of Mycobacterium ***tuberculosis*** , newer control strategies in the form of a better vaccine could decrease the global incidence of ***tuberculosis*** . A desirable trait in an effective live attenuated vaccine strain is an ability to persist within the host in a limited fashion in order to produce important protective antigens in vivo. Attenuated M. ***tuberculosis*** vaccine candidates have been constructed by deleting genes required for growth in mice. These candidate vaccines did not elicit adequate. . . to their inability to persist sufficiently long within the host tissues. Here we report that an auxotrophic mutant of M. ***tuberculosis*** defective in the de novo biosynthesis of pantothenic acid (vitamin B5) is highly attenuated in immunocompromised SCID mice and in. . . the pantothenate auxotroph survived significantly longer (250 days) than mice infected with either bacille Calmette-Guerin (BCG) vaccine or virulent M. ***tuberculosis*** (77 and 35 days, respectively). Subcutaneous immunization with this auxotroph conferred protection in C57BL/6J mice against an aerosol challenge with virulent M. ***tuberculosis*** , which was comparable with that afforded by BCG vaccination. Our findings highlight the importance of de novo pantothenate biosynthesis in limiting the intracellular survival and pathogenesis of M. ***tuberculosis*** without reducing its immunogenicity in vaccinated mice.

IT Major Concepts
Immune System (Chemical Coordination and Homeostasis); Infection
IT Diseases
tuberculosis : bacterial disease, epidemiology
Tuberculosis (MeSH)
IT Chemicals & Biochemicals
Mycobacterium ***tuberculosis*** vaccine: immunologic-drug, immunostimulant-drug; pantothenate: biosynthesis
ORGN . . .
Mammals, Rodents, Vertebrates
ORGN Classifier
Mycobacteriaceae 08881
Super Taxa
Mycobacteria; Actinomycetes and Related Organisms; Eubacteria; Bacteria; Microorganisms
Organism Name
Mycobacterium ***tuberculosis*** : auxotroph
Taxa Notes
Bacteria, Eubacteria, Microorganisms

=> e morris sheldon/au

E1	11		MORRIS SHEILA L/AU
E2	2		MORRIS SHELBY J/AU
E3	29	-->	MORRIS SHELDON/AU
E4	99		MORRIS SHELDON L/AU
E5	1		MORRIS SHELDON LEE/AU
E6	4		MORRIS SHELDON R/AU
E7	2		MORRIS SHELIA L/AU
E8	19		MORRIS SHELLI M/AU
E9	1		MORRIS SHERI/AU
E10	3		MORRIS SHERICCA/AU
E11	2		MORRIS SHERICCA W/AU
E12	2		MORRIS SHERRI/AU

=> s e3-e6 and tuberculosis

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L7         100 ("MORRIS SHELDON"/AU OR "MORRIS SHELDON L"/AU OR "MORRIS SHELDON
               LEE"/AU OR "MORRIS SHELDON R"/AU) AND TUBERCULOSIS

=> dup rem l7
PROCESSING COMPLETED FOR L7
L8           42 DUP REM L7 (58 DUPLICATES REMOVED)

=> s l8 and deletion?
L9            8 L8 AND DELETION?

=> d bib ab kwic 1-
YOU HAVE REQUESTED DATA FROM 8 ANSWERS - CONTINUE? Y/(N):y

L9   ANSWER 1 OF 8  BIOSIS  COPYRIGHT (c) 2008 The Thomson Corporation  on STN
AN   2007:540604  BIOSIS <<LOGINID::20080330>>
DN   PREV200700540913
TI   Enhanced priming of adaptive immunity by a proapoptotic mutant of
     Mycobacterium   ***tuberculosis***  .
AU   Hinchey, Joseph; Lee, Sunhee; Jeon, Bo Y.; Basaraba, Randall J.;
     Venkataswamy, Manjunatha M.; Chen, Bing; Chan, John; Braunstein, Miriam;
     Orme, Ian M.; Derrick, Steven C.;   ***Morris, Sheldon L.***  ; Jacobs,
     William R. Jr. [Reprint Author]; Porcelli, Steven A.
CS   Yeshiva Univ Albert Einstein Coll Med, Howard Hughes Med Inst, 1300 Morris
     Pk Ave, Bronx, NY 10461 USA
     jacobs@aecom.yu.edu; porcelli@aecom.yu.edu
SO   Journal of Clinical Investigation, (AUG 2007) Vol. 117, No. 8, pp.
     2279-2288.
     CODEN: JCINAO. ISSN: 0021-9738.
DT   Article
LA   English
ED   Entered STN: 17 Oct 2007
     Last Updated on STN: 17 Oct 2007
AB   The inhibition of apoptosis of infected host cells is a well-known but
     poorly understood function of pathogenic mycobacteria.  We show that
     inactivation of the secA2 gene in Mycobacterium   ***tuberculosis***  ,
     which encodes a component of a virulence-associated protein secretion
     system, enhanced the apoptosis of infected macrophages by diminishing
     secretion of mycobacterial superoxide dismutase.    ***Deletion***   of
     secA2 markedly increased priming of antigen-specific CD8(+) T cells in
     vivo, and vaccination of mice and guinea pigs with a secA2 mutant
     significantly increased resistance to M.   ***tuberculosis***   challenge
     compared with standard M. bovis bacille Calmette-Guerin vaccination.  Our
     results define a mechanism for a key immune evasion strategy of M.
       ***tuberculosis***   and provide what we believe to be a novel approach
     for improving mycobacterial vaccines.
TI   Enhanced priming of adaptive immunity by a proapoptotic mutant of
     Mycobacterium   ***tuberculosis***  .
AU.  .  .  Bo Y.; Basaraba, Randall J.; Venkataswamy, Manjunatha M.; Chen,
     Bing; Chan, John; Braunstein, Miriam; Orme, Ian M.; Derrick, Steven C.;
       ***Morris, Sheldon L.***  ; Jacobs, William R. Jr. [Reprint Author];
     Porcelli, Steven A.
AB.  .  .  is a well-known but poorly understood function of pathogenic
     mycobacteria.  We show that inactivation of the secA2 gene in
     Mycobacterium   ***tuberculosis***  , which encodes a component of a
     virulence-associated protein secretion system, enhanced the apoptosis of
     infected macrophages by diminishing secretion of mycobacterial superoxide
     dismutase.    ***Deletion***   of secA2 markedly increased priming of
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antigen-specific CD8(+) T cells in vivo, and vaccination of mice and guinea pigs with a secA2 mutant significantly increased resistance to M. ***tuberculosis*** challenge compared with standard M. bovis bacille Calmette-Guerin vaccination. Our results define a mechanism for a key immune evasion strategy of M. ***tuberculosis*** and provide what we believe to be a novel approach for improving mycobacterial vaccines.
ORGN . . .
Mammals, Rodents, Vertebrates
ORGN Classifier
Mycobacteriaceae 08881
Super Taxa
Mycobacteria; Actinomycetes and Related Organisms; Eubacteria; Bacteria; Microorganisms
Organism Name
Mycobacterium ***tuberculosis*** (species): pathogen
Mycobacterium bovis (species)
Taxa Notes
Bacteria, Eubacteria, Microorganisms
GEN Mycobacterium ***tuberculosis*** secA2 gene (Mycobacteriaceae): regulation

L9 ANSWER 2 OF 8 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
AN 2007:396670 BIOSIS <<LOGINID::20080330>>
DN PREV200700392919
TI The ESAT6 protein of Mycobacterium ***tuberculosis*** induces apoptosis of macrophages by activating caspase expression.
AU Derrick, Steven C. [Reprint Author]; ***Morris, Sheldon L.***
CS United States Food and Drug Adm, Ctr Biol Evaluat and Res, Lab Mycobacterial Dis and Cellular Immunol, Bethesda, MD 20892 USA
steven.derrick@fda.hhs.gov
SO Cellular Microbiology, (JUN 2007) Vol. 9, No. 6, pp. 1547-1555.
ISSN: 1462-5814.
DT Article
LA English
ED Entered STN: 18 Jul 2007
Last Updated on STN: 18 Jul 2007
AB The secreted Mycobacterium ***tuberculosis*** protein, ESAT6, has been studied extensively in pathogenicity and vaccine experiments. Despite these studies little is known about the function of this protein. In this report, we demonstrate that ESAT6 induces apoptosis in THP-1 human macrophages using fluorescein isothiocyanate-Annexin V and intracellular caspase staining. We show that the induction of apoptosis by ESAT6 is dependent on the dose of the protein and the expression of caspase genes. Using real-time RT-PCR, we found that expression of caspase-1, -3, -5, -7 and -8 genes was upregulated in cells treated with ESAT6 relative to untreated cells. Furthermore, we show that while infection of THP-1 cells with wild-type M. ***tuberculosis*** strain H37Rv resulted in significant apoptosis 48 h post infection, a ***deletion*** mutant that does not express ESAT6 failed to induce significant apoptosis. Finally, experimental results using a cell impermeable fluorescent stain suggests that the formation of membrane pores may be a primary mechanism by which ESAT6 evokes an apoptotic response.
TI The ESAT6 protein of Mycobacterium ***tuberculosis*** induces apoptosis of macrophages by activating caspase expression.
AU Derrick, Steven C. [Reprint Author]; ***Morris, Sheldon L.***
AB The secreted Mycobacterium ***tuberculosis*** protein, ESAT6, has been studied extensively in pathogenicity and vaccine experiments. Despite

these studies little is known about the function. . . cells treated with ESAT6 relative to untreated cells. Furthermore, we show that while infection of THP-1 cells with wild-type M. ***tuberculosis*** strain H37Rv resulted in significant apoptosis 48 h post infection, a ***deletion*** mutant that does not express ESAT6 failed to induce significant apoptosis. Finally, experimental results using a cell impermeable fluorescent stain. . .

ORGN . . .
Mammals, Primates, Vertebrates

ORGN Classifier
Mycobacteriaceae 08881

Super Taxa
Mycobacteria; Actinomycetes and Related Organisms; Eubacteria; Bacteria; Microorganisms

Organism Name
Mycobacterium ***tuberculosis*** (species): pathogen, strain-H37Rv

Taxa Notes
Bacteria, Eubacteria, Microorganisms

L9 ANSWER 3 OF 8 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
AN 2006:614816 BIOSIS <<LOGINID::20080330>>
DN PREV200600621274
TI Mycobacterium ***tuberculosis*** Delta RD1 Delta panCD: A safe and limited replicating mutant strain that protects immunocompetent and immunocompromised mice against experimental ***tuberculosis*** .
AU Sambandamurthy, Vasan K. [Reprint Author]; Derrick, Steven C.; Hsu, Tsungda; Chen, Bing; Larsen, Michelle H.; Jalapathy, Kripa V.; Chen, Mei; Kim, John; Porcelli, Steven A.; Chan, John; ***Morris, Sheldon L.*** ; Jacobs, William R. Jr.
CS US FDA, Ctr Biol Evaluat and Res, Bethesda, MD 20892 USA
jacobsw@hhmi.org
SO Vaccine, (SEP 11 2006) Vol. 24, No. 37-39, pp. 6309-6320.
CODEN: VACCDE. ISSN: 0264-410X.
DT Article
LA English
ED Entered STN: 15 Nov 2006
Last Updated on STN: 15 Nov 2006
AB The global epidemic of ***tuberculosis*** (TB), fueled by the growing HIV pandemic, warrants the development of a safe and effective vaccine against TB. We report the construction and characterization of an unlinked double ***deletion*** mutant of Mycobacterium ***tuberculosis*** H37Rv that deletes both the primary attenuating mutation of BCG (Delta RD1) and two genes required for the synthesis of pantothenate (Delta panCD). The M. ***tuberculosis*** Delta RD1 Delta panCD (mc(2)6030) mutant undergoes limited replication in mice, and yet is both significantly safer than BCG in immunocompromised mice and also safe in guinea pigs. Additionally, the mc(2)6030 strain does not reactivate in a mouse chemo-immunosuppression model. Importantly, long-lived protective immune responses following immunization with the mc(2)6030 strain prolong the survival of wild type mice, and CD4-deficient mice against an aerosol challenge with virulent M. ***tuberculosis*** . Given its overall safety and effectiveness, the mc(2)6030 live attenuated strain should be considered as a human vaccine candidate for protecting both healthy and HIV-infected individuals against TB. (c) 2006 Elsevier Ltd. All rights reserved.
TI Mycobacterium ***tuberculosis*** Delta RD1 Delta panCD: A safe and limited replicating mutant strain that protects immunocompetent and

immunocompromised mice against experimental ***tuberculosis*** .

AU. . . C.; Hsu, Tsungda; Chen, Bing; Larsen, Michelle H.; Jalapathy, Kripa V.; Chen, Mei; Kim, John; Porcelli, Steven A.; Chan, John; ***Morris,*** *** Sheldon L.*** ; Jacobs, William R. Jr.

AB The global epidemic of ***tuberculosis*** (TB), fueled by the growing HIV pandemic, warrants the development of a safe and effective vaccine against TB. We report the construction and characterization of an unlinked double ***deletion*** mutant of Mycobacterium ***tuberculosis*** H37Rv that deletes both the primary attenuating mutation of BCG (Delta RD1) and two genes required for the synthesis of pantothenate (Delta panCD). The M. ***tuberculosis*** Delta RD1 Delta panCD (mc(2)6030) mutant undergoes limited replication in mice, and yet is both significantly safer than BCG in. . . the mc(2)6030 strain prolong the survival of wild type mice, and CD4-deficient mice against an aerosol challenge with virulent M. ***tuberculosis*** . Given its overall safety and effectiveness, the mc(2)6030 live attenuated strain should be considered as a human vaccine candidate for. . .

IT Major Concepts
Pharmacology; Infection; Immune System (Chemical Coordination and Homeostasis)

IT Diseases
experimental ***tuberculosis*** : bacterial disease, infectious disease, prevention and control

IT Chemicals & Biochemicals
CD4; ***tuberculosis*** vaccine: immunologic-drug, immunostimulant-drug

ORGN . . .
Mammals, Rodents, Vertebrates

ORGN Classifier
Mycobacteriaceae 08881

Super Taxa
Mycobacteria; Actinomycetes and Related Organisms; Eubacteria; Bacteria; Microorganisms

Organism Name
Mycobacterium ***tuberculosis*** (species): pathogen, strain-H37Rv, strain-delta-RD1, strain-delta-panCD, strain-mc-2-6030, strain-BCG Pasteur, strain-Erdman

Taxa Notes
Bacteria, Eubacteria, Microorganisms

ORGN Classifier
Retroviridae 03305

Super Taxa

L9 ANSWER 4 OF 8 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN

AN 2003:578657 BIOSIS <<LOGINID::20080330>>

DN PREV200300584283

TI The primary mechanism of attenuation of bacillus Calmette-Guerin is a loss of secreted lytic function required for invasion of lung interstitial tissue.

AU Hsu, Tsungda; Hingley-Wilson, Suzanne M.; Chen, Bing; Chen, Mei; Dai, Annie Z.; Morin, Paul M.; Marks, Carolyn B.; Padiyar, Jeevan; Goulding, Celia; Gingery, Mari; Eisenberg, David; Russell, Robert G.; Derrick, Steven C.; Collins, Frank M.; ***Morris, Sheldon L.*** ; King, C. Harold; Jacobs, William R. Jr. [Reprint Author]

CS Department of Pathology, Howard Hughes Medical Institute, Albert Einstein College of Medicine, Bronx, NY, 10461, USA
jacobsw@hhmi.org

SO Proceedings of the National Academy of Sciences of the United States of America, (October 14 2003) Vol. 100, No. 21, pp. 12420-12425. print. ISSN: 0027-8424 (ISSN print).
DT Article
LA English
ED Entered STN: 10 Dec 2003
Last Updated on STN: 10 Dec 2003
AB ***Tuberculosis*** remains a leading cause of death worldwide, despite the availability of effective chemotherapy and a vaccine. Bacillus Calmette-Guerin (BCG), the ***tuberculosis*** vaccine, is an attenuated mutant of Mycobacterium bovis that was isolated after serial subcultures, yet the functional basis for this attenuation has never been elucidated. A single region (RD1), which is absent in all BCG substrains, was deleted from virulent M. bovis and Mycobacterium ***tuberculosis*** strains, and the resulting DELTARD1 mutants were significantly attenuated for virulence in both immunocompromised and immunocompetent mice. The M. ***tuberculosis*** DELTARD1 mutants were also shown to protect mice against aerosol challenge, in a similar manner to BCG. Interestingly, the DELTARD1 mutants failed to cause cytolysis of pneumocytes, a phenotype that had been previously used to distinguish virulent M. ***tuberculosis*** from BCG. A specific transposon mutation, which disrupts the Rv3874 Rv3875 (cfp-10 esat-6) operon of RD1, also caused loss of the cytolytic phenotype in both pneumocytes and macrophages. This mutation resulted in the attenuation of virulence in mice, as the result of reduced tissue invasiveness. Moreover, specific ***deletion*** of each transcriptional unit of RD1 revealed that three independent transcriptional units are required for virulence, two of which are involved in the secretion of ESAT-6 (6-kDa early secretory antigenic target). We conclude that the primary attenuating mechanism of bacillus Calmette-Guerin is the loss of cytolytic activity mediated by secreted ESAT-6, which results in reduced tissue invasiveness.
AU. . . Marks, Carolyn B.; Padiyar, Jeevan; Goulding, Celia; Gingery, Mari; Eisenberg, David; Russell, Robert G.; Derrick, Steven C.; Collins, Frank M.; ***Morris, Sheldon L.*** ; King, C. Harold; Jacobs, William R. Jr. [Reprint Author]
AB ***Tuberculosis*** remains a leading cause of death worldwide, despite the availability of effective chemotherapy and a vaccine. Bacillus Calmette-Guerin (BCG), the ***tuberculosis*** vaccine, is an attenuated mutant of Mycobacterium bovis that was isolated after serial subcultures, yet the functional basis for this. . . elucidated. A single region (RD1), which is absent in all BCG substrains, was deleted from virulent M. bovis and Mycobacterium ***tuberculosis*** strains, and the resulting DELTARD1 mutants were significantly attenuated for virulence in both immunocompromised and immunocompetent mice. The M. ***tuberculosis*** DELTARD1 mutants were also shown to protect mice against aerosol challenge, in a similar manner to BCG. Interestingly, the DELTARD1 mutants failed to cause cytolysis of pneumocytes, a phenotype that had been previously used to distinguish virulent M. ***tuberculosis*** from BCG. A specific transposon mutation, which disrupts the Rv3874 Rv3875 (cfp-10 esat-6) operon of RD1, also caused loss of. . . macrophages. This mutation resulted in the attenuation of virulence in mice, as the result of reduced tissue invasiveness. Moreover, specific ***deletion*** of each transcriptional unit of RD1 revealed that three independent transcriptional units are required for virulence, two of which are. . .
IT . . .
Infection; Pharmaceuticals (Pharmacology); Respiratory System

(Respiration)
IT Parts, Structures, & Systems of Organisms
lung: respiratory system, interstitial tissue
IT Diseases
tuberculosis : bacterial disease
Tuberculosis (MeSH)
IT Chemicals & Biochemicals
BCG: vaccine
ORGN . . .
ORGN Classifier
Mycobacteriaceae 08881
Super Taxa
Mycobacteria; Actinomycetes and Related Organisms; Eubacteria;
Bacteria; Microorganisms
Organism Name
Mycobacterium bovis (species): pathogen
Mycobacterium ***tuberculosis*** (species): pathogen
Taxa Notes
Bacteria, Eubacteria, Microorganisms

L9 ANSWER 5 OF 8 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
AN 1995:547995 BIOSIS <<LOGINID::20080330>>
DN PREV199698562295
TI Characterization of the katG and inhA genes of isoniazid-resistant clinical isolates of Mycobacterium ***tuberculosis*** .
AU Rouse, David A.; Li, Zhongming; Bai, Gil-Han; ***Morris, Sheldon L.*** [Reprint author]
CS Lab. Mycobacteria, FDA/CBER, HFM-431, 8800 Rockville Pike, Bethesda, MD 20892, USA
SO Antimicrobial Agents and Chemotherapy, (1995) Vol. 39, No. 11, pp. 2472-2477.
CODEN: AMACCQ. ISSN: 0066-4804.
DT Article
LA English
ED Entered STN: 31 Dec 1995
Last Updated on STN: 28 Feb 1996
AB Resistance to isoniazid in Mycobacterium ***tuberculosis*** has been associated with mutations in genes encoding the mycobacterial catalase-peroxidase (katG) and the inhA protein (inhA). Among the 26 isoniazid-resistant clinical isolates evaluated in this study, mutations in putative inhA regulatory sequences were identified in 2 catalase-positive isolates, katG gene alterations were detected in 20 strains. and 4 isolates had wild-type katG and inhA genes. Mutations in the katG gene were detected in all II catalase-negative isolates: one frameshift insertion, two partial gene ***deletions*** , and nine different missense mutations were identified. An arginine-to-leucine substitution at position 463 was detected in nine catalase-positive isolates. However, site-directed mutagenesis experiments demonstrated that the presence of a leucine at codon 463 did not alter the activity of the M. ***tuberculosis*** catalase-peroxidase and did not affect the capacity of this enzyme to restore isoniazid susceptibility to isoniazid-resistant, KatG-defective Mycobacterium smegmatis BH1 cells. These studies further support the association between katG and inhA gene mutations and isoniazid resistance in M. ***tuberculosis*** , while also suggesting that other undefined mechanisms of isoniazid resistance exist.
TI Characterization of the katG and inhA genes of isoniazid-resistant

clinical isolates of Mycobacterium ***tuberculosis*** .

AU Rouse, David A.; Li, Zhongming; Bai, Gil-Han; ***Morris, Sheldon L.*** [Reprint author]

AB Resistance to isoniazid in Mycobacterium ***tuberculosis*** has been associated with mutations in genes encoding the mycobacterial catalase-peroxidase (katG) and the inhA protein (inhA). Among the 26. . . inhA genes. Mutations in the katG gene were detected in all II catalase-negative isolates: one frameshift insertion, two partial gene ***deletions*** , and nine different missense mutations were identified. An arginine-to-leucine substitution at position 463 was detected in nine catalase-positive isolates. However,. . . mutagenesis experiments demonstrated that the presence of a leucine at codon 463 did not alter the activity of the M. ***tuberculosis*** catalase-peroxidase and did not affect the capacity of this enzyme to restore isoniazid susceptibility to isoniazid-resistant, KatG-defective Mycobacterium smegmatis BH1 cells. These studies further support the association between katG and inhA gene mutations and isoniazid resistance in M. ***tuberculosis*** , while also suggesting that other undefined mechanisms of isoniazid resistance exist.

ORGN Classifier
Mycobacteriaceae 08881
Super Taxa
Mycobacteria; Actinomycetes and Related Organisms; Eubacteria; Bacteria; Microorganisms
Organism Name
Mycobacterium ***tuberculosis***
Taxa Notes
Bacteria, Eubacteria, Microorganisms

L9 ANSWER 6 OF 8 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN

AN 1995:217200 BIOSIS <<LOGINID::20080330>>

DN PREV199598231500

TI Molecular mechanisms of isoniazid resistance in Mycobacterium ***tuberculosis*** and Mycobacterium bovis.

AU Rouse, David A. [Reprint author]; ***Morris, Sheldon L.***

CS Lab. Mycobacteria, Cent. Biologics Evaluation Res., Food Drug Adm., 8800 Rockvile Pike, Bethesda, MD 20892, USA

SO Infection and Immunity, (1995) Vol. 63, No. 4, pp. 1427-1433. CODEN: INFIBR. ISSN: 0019-9567.

DT Article

LA English

ED Entered STN: 31 May 1995
Last Updated on STN: 1 Jun 1995

AB Genetic and biochemical studies have suggested a link between reduced catalase activity and resistance to isoniazid in Mycobacterium ***tuberculosis*** . In this study, we examined the molecular mechanisms of resistance to isoniazid with six in vitro mutants of the M. ***tuberculosis*** complex (Mycobacterium bovis and M. ***tuberculosis***). Five of six mutants resistant to isoniazid were negative by catalase assays. Immunoblot analyses using a polyclonal antibody against the katG gene product (catalase-peroxidase) demonstrated that the enzyme is not produced in four of these isoniazid-resistant strains. A complete ***deletion*** of the katG gene was detected in only one of these isoniazid-resistant M. ***tuberculosis*** complex strains by Southern blot analyses. In two other resistant strains, partial ***deletions*** of the katG gene were identified. A point

mutation which resulted in the insertion of a termination codon in the katG coding sequence caused a catalase-negative phenotype in a fourth strain. Of the two resistant strains which produce the enzyme, one was shown to be negative by a catalase assay. Single-stranded conformational polymorphism and DNA sequence analyses identified a mutation in the katG gene of this strain which may contribute to reduced enzymatic activity and subsequent isoniazid resistance. These data demonstrate that genetic alterations to the katG gene other than complete ***deletions*** are prevalent and may contribute significantly to the number of cases of isoniazid-resistant ***tuberculosis*** .

TI Molecular mechanisms of isoniazid resistance in Mycobacterium ***tuberculosis*** and Mycobacterium bovis.

AU Rouse, David A. [Reprint author]; ***Morris, Sheldon L.***

AB Genetic and biochemical studies have suggested a link between reduced catalase activity and resistance to isoniazid in Mycobacterium ***tuberculosis*** . In this study, we examined the molecular mechanisms of resistance to isoniazid with six in vitro mutants of the M. ***tuberculosis*** complex (Mycobacterium bovis and M. ***tuberculosis***). Five of six mutants resistant to isoniazid were negative by catalase assays. Immunoblot analyses using a polyclonal antibody against the katG gene product (catalase-peroxidase) demonstrated that the enzyme is not produced in four of these isoniazid-resistant strains. A complete ***deletion*** of the katG gene was detected in only one of these isoniazid-resistant M. ***tuberculosis*** complex strains by Southern blot analyses. In two other resistant strains, partial ***deletions*** of the katG gene were identified. A point mutation which resulted in the insertion of a termination codon in the. . . reduced enzymatic activity and subsequent isoniazid resistance. These data demonstrate that genetic alterations to the katG gene other than complete ***deletions*** are prevalent and may contribute significantly to the number of cases of isoniazid-resistant ***tuberculosis*** .

ORGN . . .
Primates, Vertebrates

ORGN Classifier
Mycobacteriaceae 08881

Super Taxa
Mycobacteria; Actinomycetes and Related Organisms; Eubacteria; Bacteria; Microorganisms

Organism Name
Mycobacterium bovis
Mycobacterium ***tuberculosis***

Taxa Notes
Bacteria, Eubacteria, Microorganisms

L9 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2004:648328 CAPLUS <<LOGINID::20080330>>

DN 141:172863

TI Mycobacterial vaccine comprising ***deletion*** mutagenesis in RD1 region, and vitamin and amino acid production-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes

IN Bardarov, Stoyan; Jacobs, William R., Jr.; Hsu, Tsungda; Sambandamurthy, Vasan; ***Morris, Sheldon***

PA Albert Einstein College of Medicine of Yeshiva University, USA

SO PCT Int. Appl., 116 pp.
CODEN: PIXXD2

DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004066928	A2	20040812	WO 2004-US1773	20040123
	WO 2004066928	A3	20060105		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	US 2007202131	A1	20070830	US 2007-542958	20070130
PRAI	US 2003-442631P	P	20030124		
	WO 2004-US1773	W	20040123		

AB Methods of treating a mammal that is deficient in CD4+ and/or CD8+ lymphocytes are provided. The methods comprise inoculating the mammal with an attenuated mycobacterium in the M. ***tuberculosis*** complex. In these methods, the mycobacterium comprises two ***deletions*** , wherein a virulent mycobacterium in the M. ***tuberculosis*** complex having either ***deletion*** exhibits attenuated virulence. The two ***deletions*** is a ***deletion*** of RD1 region, region controlling prodn. of vitamin (e.g. pantothenic acid or NAD), and region controlling prodn. of amino acid (e.g. proline, tryptophan, leucine, or lysin). The ***deletion*** is .DELTA.panCD ***deletion*** and .DELTA.lysA ***deletion*** . Use of these mycobacteria for the manuf. of a medicament for the treatment of mammals deficient in CD4+ and/or CD8+ lymphocytes is also provided.

TI Mycobacterial vaccine comprising ***deletion*** mutagenesis in RD1 region, and vitamin and amino acid production-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes

IN Bardarov, Stoyan; Jacobs, William R., Jr.; Hsu, Tsungda; Sambandamurthy, Vasan; ***Morris, Sheldon***

AB . . . in CD4+ and/or CD8+ lymphocytes are provided. The methods comprise inoculating the mammal with an attenuated mycobacterium in the M. ***tuberculosis*** complex. In these methods, the mycobacterium comprises two ***deletions*** , wherein a virulent mycobacterium in the M. ***tuberculosis*** complex having either ***deletion*** exhibits attenuated virulence. The two ***deletions*** is a ***deletion*** of RD1 region, region controlling prodn. of vitamin (e.g. pantothenic acid or NAD), and region controlling prodn. of amino acid (e.g. proline, tryptophan, leucine, or lysin). The ***deletion*** is .DELTA.panCD ***deletion*** and .DELTA.lysA ***deletion*** . Use of these mycobacteria for the manuf. of a medicament for the treatment of mammals deficient in CD4+ and/or CD8+. . .

ST Mycobacterium ***tuberculosis*** complex ***deletion*** RD1 vitamin amino acid prodn; mycobacterial vaccine RD1 panCD lysA ***deletion*** CD4 CD8 lymphocyte

IT Mycobacterium ***tuberculosis***
(H37Rv and CDC1551 strains; mycobacterial vaccine comprising ***deletion*** mutagenesis in RD1 region, and vitamin and amino acid

prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

IT Genetic element
RL: BSU (Biological study, unclassified); PRP (Properties); REM (Removal or disposal); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(RD1 region; mycobacterial vaccine comprising ***deletion*** mutagenesis in RD1 region, and vitamin and amino acid prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

IT Vaccines
(antimalarial; mycobacterial vaccine comprising ***deletion*** mutagenesis in RD1 region, and vitamin and amino acid prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

IT Development, mammalian postnatal
(child; mycobacterial vaccine comprising ***deletion*** mutagenesis in RD1 region, and vitamin and amino acid prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

IT Toxoids
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(diphtheria; mycobacterial vaccine comprising ***deletion*** mutagenesis in RD1 region, and vitamin and amino acid prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

IT Steroids, biological studies
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(enzyme; mycobacterial vaccine comprising ***deletion*** mutagenesis in RD1 region, and vitamin and amino acid prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

IT DNA
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(foreign; mycobacterial vaccine comprising ***deletion*** mutagenesis in RD1 region, and vitamin and amino acid prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

IT Venoms
(insect; mycobacterial vaccine comprising ***deletion*** mutagenesis in RD1 region, and vitamin and amino acid prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

IT Development, microbial
(merozoite, malarial; mycobacterial vaccine comprising ***deletion*** mutagenesis in RD1 region, and vitamin and amino acid prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

IT Borrelia
Bos taurus
CD4-positive T cell
CD8-positive T cell

DNA sequences
Genetic engineering
Herpesviridae
Human
Human herpesvirus
Human immunodeficiency virus
Human poliovirus
Immunostimulants
Leishmania
Mammalia
Measles virus
Molecular cloning
Mumps virus
Mycobacterium
Mycobacterium africanum
Mycobacterium avium
Mycobacterium bovis
Mycobacterium intracellulare
Mycobacterium leprae
Neisseria
Pertussis
Rabies virus
Salmonella
Shigella
Transduction, genetic
Treponema
Tuberculosis
Vibrio cholerae
(mycobacterial vaccine comprising ***deletion*** mutagenesis in RD1 region, and vitamin and amino acid prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

IT Antigens
Enzymes, biological studies
Interleukin 1
Interleukin 2
Interleukin 3
Interleukin 4
Interleukin 5
Interleukin 6
Interleukin 7
Lymphokines
Lymphotoxin
Peptides, biological studies
Proteins
Tumor necrosis factors
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(mycobacterial vaccine comprising ***deletion*** mutagenesis in RD1 region, and vitamin and amino acid prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

IT Reporter gene
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(mycobacterial vaccine comprising ***deletion*** mutagenesis in RD1 region, and vitamin and amino acid prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

IT Amino acids, biological studies

Vitamins
RL: BSU (Biological study, unclassified); REM (Removal or disposal); BIOL (Biological study); PROC (Process)
(mycobacterial vaccine comprising ***deletion*** mutagenesis in RD1 region, and vitamin and amino acid prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

IT Molecules
(reporter; mycobacterial vaccine comprising ***deletion*** mutagenesis in RD1 region, and vitamin and amino acid prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

IT Gene, microbial
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(sacB; mycobacterial vaccine comprising ***deletion*** mutagenesis in RD1 region, and vitamin and amino acid prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

IT Genetic markers
(selective; mycobacterial vaccine comprising ***deletion*** mutagenesis in RD1 region, and vitamin and amino acid prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

IT Recombination, genetic
(sequential two-step; mycobacterial vaccine comprising ***deletion*** mutagenesis in RD1 region, and vitamin and amino acid prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

IT Immunodeficiency
(severe combined, without; mycobacterial vaccine comprising ***deletion*** mutagenesis in RD1 region, and vitamin and amino acid prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

IT Mutagenesis
(site-directed, ***deletion*** ; mycobacterial vaccine comprising ***deletion*** mutagenesis in RD1 region, and vitamin and amino acid prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

IT Venoms
(snake; mycobacterial vaccine comprising ***deletion*** mutagenesis in RD1 region, and vitamin and amino acid prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

IT Development, microbial
(sporozoite, malarial; mycobacterial vaccine comprising ***deletion*** mutagenesis in RD1 region, and vitamin and amino acid prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

IT Malaria
(sporozoites and merozoites; mycobacterial vaccine comprising ***deletion*** mutagenesis in RD1 region, and vitamin and amino acid prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

IT Vaccines
(synthetic; mycobacterial vaccine comprising ***deletion*** mutagenesis in RD1 region, and vitamin and amino acid prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

IT Toxoids

RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(tetanus; mycobacterial vaccine comprising ***deletion*** mutagenesis in RD1 region, and vitamin and amino acid prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

IT Antimalarials
(vaccines; mycobacterial vaccine comprising ***deletion*** mutagenesis in RD1 region, and vitamin and amino acid prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

IT Insecta
(venom; mycobacterial vaccine comprising ***deletion*** mutagenesis in RD1 region, and vitamin and amino acid prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

IT Interferons
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(.alpha.; mycobacterial vaccine comprising ***deletion*** mutagenesis in RD1 region, and vitamin and amino acid prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

IT Interferons
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(.beta.; mycobacterial vaccine comprising ***deletion*** mutagenesis in RD1 region, and vitamin and amino acid prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

IT Interferons
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(.gamma.; mycobacterial vaccine comprising ***deletion*** mutagenesis in RD1 region, and vitamin and amino acid prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

IT Genetic element
RL: BSU (Biological study, unclassified); PRP (Properties); REM (Removal or disposal); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(.DELTA.lysA; mycobacterial vaccine comprising ***deletion*** mutagenesis in RD1 region, and vitamin and amino acid prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

IT Genetic element
RL: BSU (Biological study, unclassified); PRP (Properties); REM (Removal or disposal); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(.DELTA.panCD; mycobacterial vaccine comprising ***deletion*** mutagenesis in RD1 region, and vitamin and amino acid prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

IT 51923-03-6, Catechol dehydrogenase

RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(Catechol dehydrogenase; mycobacterial vaccine comprising ***deletion*** mutagenesis in RD1 region, and vitamin and amino acid prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

IT 9001-45-0, .beta.-Glucuronidase 9031-11-2, .beta.-Galactosidase
RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(mycobacterial vaccine comprising ***deletion*** mutagenesis in RD1 region, and vitamin and amino acid prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

IT 53-84-9, NAD 56-87-1, L-Lysine, biological studies 61-90-5, L-Leucine, biological studies 73-22-3, L-Tryptophan, biological studies 79-83-4, Pantothenic acid 147-85-3, L-Proline, biological studies 9014-00-0, Luciferase
RL: BSU (Biological study, unclassified); REM (Removal or disposal); BIOL (Biological study); PROC (Process)
(mycobacterial vaccine comprising ***deletion*** mutagenesis in RD1 region, and vitamin and amino acid prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

IT 735844-96-9 735847-33-3 735847-34-4 735847-35-5
RL: BSU (Biological study, unclassified); PRP (Properties); REM (Removal or disposal); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(nucleotide sequence; mycobacterial vaccine comprising ***deletion*** mutagenesis in RD1 region, and vitamin and amino acid prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

IT 735861-33-3 735861-34-4 735861-36-6 735861-37-7 735861-38-8 735861-39-9 735861-40-2 735861-41-3
RL: PRP (Properties)
(unclaimed nucleotide sequence; mycobacterial vaccine comprising ***deletion*** mutagenesis in RD1 region, and vitamin and amino acid prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

L9 ANSWER 8 OF 8 MEDLINE on STN
AN 2002736603 MEDLINE <<LOGINID::20080330>>
DN PubMed ID: 12499190
TI Exploring the structure and function of the mycobacterial KatG protein using trans-dominant mutants.
AU DeVito Joseph A; ***Morris Sheldon***
CS Laboratory of Mycobacterial Diseases and Cellular Immunology, Center for Biologics Evaluation and Research, U.S. Food and Drug Administration, Bethesda, Maryland 19880, USA.
SO Antimicrobial agents and chemotherapy, (2003 Jan) Vol. 47, No. 1, pp. 188-95.
Journal code: 0315061. ISSN: 0066-4804.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)
LA English
FS Priority Journals
EM 200306
ED Entered STN: 27 Dec 2002
Last Updated on STN: 4 Jun 2003

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     Entered Medline: 3 Jun 2003
AB   In order to probe the structure and function of the mycobacterial
     catalase-peroxidase enzyme (KatG), we employed a genetic approach using
     dominant-negative analysis of katG merodiploids.  Transformation of
     Mycobacterium bovis BCG with various katG point mutants (expressed from
     low-copy-number plasmids) resulted in reductions in peroxidase and
     catalase activities as measured in cell extracts.  These reductions in
     enzymatic activity usually correlated with increased resistance to the
     antituberculosis drug isoniazid (INH).  However, for the N138S
     trans-dominant mutant, the catalase-peroxidase activity was significantly
     decreased while the sensitivity to INH was retained. trans-dominance
     required katG expression from multicopy plasmids and could not be
     demonstrated with katG mutants integrated elsewhere on the wild-type M.
     bovis BCG chromosome.  Reversal of the mutant phenotype through plasmid
     exchange suggested the catalase-peroxidase deficiency occurred at the
     protein level and that INH resistance was not due to a second site
     mutation(s).  Electrophoretic analysis of KatG proteins from the
     trans-dominant mutants showed a reduction in KatG dimers compared to WT
     and formation of heterodimers with reduced activity.  The mutants
     responsible for these defects cluster around proposed active site
     residues: N138S, T275P, S315T, and D381G.  In an attempt to identify
     mutants that might delimit the region(s) of KatG involved in subunit
     interactions, C-terminal truncations were constructed (with and without
     the D381G dominant-negative mutation).  None of the C-terminal
       ***deletions***   were able to complement a DeltakatG strain, nor could
     they cause a dominant-negative effect on the WT.  Taken together, these
     results suggest an intricate association between the amino- and
     carboxy-terminal regions of KatG and may be consistent with a
     domain-swapping mechanism for KatG dimer formation.
AU   DeVito Joseph A;   ***Morris Sheldon***
AB   .  .  .  KatG involved in subunit interactions, C-terminal truncations
     were constructed (with and without the D381G dominant-negative mutation).
     None of the C-terminal   ***deletions***   were able to complement a
     DeltakatG strain, nor could they cause a dominant-negative effect on the
     WT.  Taken together, these.  .  .
CT   .  .  .  Catalase: PH, physiology
      Electrophoresis, Agar Gel
     *Escherichia coli Proteins: GE, genetics
      Escherichia coli Proteins: PH, physiology
      Microbial Sensitivity Tests
     *Mutation
         *** Mycobacterium tuberculosis: DE, drug effects***
         ****Mycobacterium tuberculosis: GE, genetics***
      Peroxidase: ME, metabolism
      Phenotype


=> e bardarov stoyan/au
E1          14     BARDAROV S S/AU
E2           2     BARDAROV SAVCO/AU
E3          27 --> BARDAROV STOYAN/AU
E4           7     BARDAROV STOYAN S/AU
E5           8     BARDAROV SVETOSLAV/AU
E6           7     BARDAROV SVETOSLAV JR/AU
E7           1     BARDAROV SVETOSLAV S JR/AU
E8           3     BARDAROV SVETSOSLAV/AU
E9          21     BARDAROV V/AU
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E10          1     BARDAROVA K/AU
E11          1     BARDAROVA K G/AU
E12          1     BARDAROVA V/AU

=> s e1-e4 and tuberculosis
L10         34 ("BARDAROV S S"/AU OR "BARDAROV SAVCO"/AU OR "BARDAROV STOYAN"/A
               U OR "BARDAROV STOYAN S"/AU) AND TUBERCULOSIS

=> dup rem l10
PROCESSING COMPLETED FOR L10
L11          19 DUP REM L10 (15 DUPLICATES REMOVED)

=> d bib ab kwic 1-
YOU HAVE REQUESTED DATA FROM 19 ANSWERS - CONTINUE? Y/(N):y

L11  ANSWER 1 OF 19  CAPLUS  COPYRIGHT 2008 ACS on STN
AN   2004:648328  CAPLUS <<LOGINID::20080330>>
DN   141:172863
TI   Mycobacterial vaccine comprising deletion mutagenesis in RD1 region, and
     vitamin and amino acid production-controlling regions for treating mammal
     deficient in CD4+ and/or CD8+ lymphocytes
IN     ***Bardarov, Stoyan***  ; Jacobs, William R., Jr.; Hsu, Tsungda;
     Sambandamurthy, Vasan; Morris, Sheldon
PA   Albert Einstein College of Medicine of Yeshiva University, USA
SO   PCT Int. Appl., 116 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
     ---------------     ----   --------    --------------------   --------
PI   WO 2004066928        A2    20040812    WO 2004-US1773         20040123
     WO 2004066928        A3    20060105
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
             NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
             TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
             IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM,
             GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW,
             MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
     US 2007202131        A1    20070830    US 2007-542958         20070130
PRAI US 2003-442631P      P     20030124
     WO 2004-US1773       W     20040123
AB   Methods of treating a mammal that is deficient in CD4+ and/or CD8+
     lymphocytes are provided.  The methods comprise inoculating the mammal
     with an attenuated mycobacterium in the M.   ***tuberculosis***   complex.
     In these methods, the mycobacterium comprises two deletions, wherein a
     virulent mycobacterium in the M.   ***tuberculosis***   complex having
     either deletion exhibits attenuated virulence.  The two deletions is a
     deletion of RD1 region, region controlling prodn. of vitamin (e.g.
     pantothenic acid or NAD), and region controlling prodn. of amino acid
     (e.g. proline, tryptophan, leucine, or lysin).  The deletion is
     .DELTA.panCD deletion and .DELTA.lysA deletion.  Use of these mycobacteria
     for the manuf. of a medicament for the treatment of mammals deficient in
```

CD4+ and/or CD8+ lymphocytes is also provided.

IN ***Bardarov, Stoyan*** ; Jacobs, William R., Jr.; Hsu, Tsungda; Sambandamurthy, Vasan; Morris, Sheldon

AB . . . in CD4+ and/or CD8+ lymphocytes are provided. The methods comprise inoculating the mammal with an attenuated mycobacterium in the M. ***tuberculosis*** complex. In these methods, the mycobacterium comprises two deletions, wherein a virulent mycobacterium in the M. ***tuberculosis*** complex having either deletion exhibits attenuated virulence. The two deletions is a deletion of RD1 region, region controlling prodn. of. . .

ST Mycobacterium ***tuberculosis*** complex deletion RD1 vitamin amino acid prodn; mycobacterial vaccine RD1 panCD lysA deletion CD4 CD8 lymphocyte

IT Mycobacterium ***tuberculosis***
(H37Rv and CDC1551 strains; mycobacterial vaccine comprising deletion mutagenesis in RD1 region, and vitamin and amino acid prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

IT Borrelia
Bos taurus
CD4-positive T cell
CD8-positive T cell
DNA sequences
Genetic engineering
Herpesviridae
Human
Human herpesvirus
Human immunodeficiency virus
Human poliovirus
Immunostimulants
Leishmania
Mammalia
Measles virus
Molecular cloning
Mumps virus
Mycobacterium
Mycobacterium africanum
Mycobacterium avium
Mycobacterium bovis
Mycobacterium intracellulare
Mycobacterium leprae
Neisseria
Pertussis
Rabies virus
Salmonella
Shigella
Transduction, genetic
Treponema
Tuberculosis
Vibrio cholerae
(mycobacterial vaccine comprising deletion mutagenesis in RD1 region, and vitamin and amino acid prodn.-controlling regions for treating mammal deficient in CD4+ and/or CD8+ lymphocytes)

L11 ANSWER 2 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2003:678598 CAPLUS <<LOGINID::20080330>>

DN 139:212868

TI Attenuated Mycobacterium ***tuberculosis*** vaccines comprising deletion of RD1 region

IN Jacobs, William R., Jr.; Hsu, Tsungda; ***Bardarov, Stoyan*** ; Sambandamurthy, Vasan

PA Albert Einstein College of Medicine of Yeshiva University, USA

SO PCT Int. Appl., 102 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003070164	A2	20030828	WO 2003-US2046	20030124
	WO 2003070164	A3	20060216		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	AU 2003209345	A1	20030909	AU 2003-209345	20030124
PRAI	US 2002-358152P	P	20020219		
	WO 2003-US2046	W	20030124		

AB Non-naturally occurring mycobacteria in the Mycobacterium ***tuberculosis*** complex are provided. These mycobacteria have a deletion of an RD1 region or a region controlling prodn. of a vitamin, and exhibit attenuated virulence in a mammal when compared to the mycobacteria without the deletion. Also provided are non-naturally occurring mycobacteria that have a deletion of a region controlling prodn. of lysine, and mycobacteria comprising two attenuating deletions. Vaccines comprising these mycobacteria are also provided, as are methods of protecting mammals from virulent mycobacteria using the vaccines. Also provided are methods of prepg. these vaccines which include the step of deleting an RD1 region or a region controlling prodn. of a vitamin from a mycobacterium in the M ***tuberculosis*** complex.

TI Attenuated Mycobacterium ***tuberculosis*** vaccines comprising deletion of RD1 region

IN Jacobs, William R., Jr.; Hsu, Tsungda; ***Bardarov, Stoyan*** ; Sambandamurthy, Vasan

AB Non-naturally occurring mycobacteria in the Mycobacterium ***tuberculosis*** complex are provided. These mycobacteria have a deletion of an RD1 region or a region controlling prodn. of a vitamin,. . . . step of deleting an RD1 region or a region controlling prodn. of a vitamin from a mycobacterium in the M ***tuberculosis*** complex.

ST Mycobacterium ***tuberculosis*** vitamin pantothenic acid NAD RD1 region deletion; antigen vaccine Mycobacterium ***tuberculosis*** RD1 deletion

IT Borrelia
Bos taurus
DNA sequences
Genetic engineering
Genetic markers
Herpesviridae

Human
Human immunodeficiency virus
Human poliovirus
Immunodeficiency
Immunostimulants
Infection
Leishmania
Mammalia
Measles virus
Molecular cloning
Mumps virus
Mus
Mycobacterium BCG
Mycobacterium africanum
Mycobacterium avium
Mycobacterium bovis
Mycobacterium intracellulare
Mycobacterium leprae
Mycobacterium ***tuberculosis***
Neisseria
Pertussis
Rabies
Recombination, genetic
Salmonella
Shigella
Transduction, genetic
Treponema
Vaccines
Vibrio cholerae
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Vitamins
RL: BSU (Biological study, unclassified); REM (Removal or disposal); BIOL (Biological study); PROC (Process)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Antigens
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Enzymes, biological studies
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Interleukin 1
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Interleukin 2
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Interleukin 3

RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Interleukin 4
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Interleukin 5
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Interleukin 6
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Interleukin 7
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Lymphokines
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Lymphotoxin
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Reporter gene
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Tumor necrosis factors
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Microorganism
(auxotrophic; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Development, mammalian postnatal
(child; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Toxoids
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(diphtheria; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Steroids, biological studies
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)
(enzyme; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Drug delivery systems
(injections, s.c.; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Venoms
(insect; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Drug delivery systems
(intradermal; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Development, microbial
(merozoite, malaria; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT DNA
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(recombinant; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Gene, microbial
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(sacB; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Mutagenesis
(site-directed, deletion; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Venoms
(snake; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Development, microbial
(sporozoite, malaria; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Toxoids
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tetanus; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT ***Tuberculosis***
(vaccine; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Insecta
(venom; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Interferons
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.alpha.; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Interferons
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.beta.; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT Interferons
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)
(.gamma.; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT 53-84-9, Nicotinamide adenine dinucleotide 56-87-1, L-Lysine, biological studies 61-90-5, L-Leucine, biological studies 73-22-3, L-Tryptophan, biological studies 79-83-4, Pantothenic acid 147-85-3, L-Proline, biological studies
RL: BSU (Biological study, unclassified); REM (Removal or disposal); BIOL (Biological study); PROC (Process)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT 9001-45-0, .beta. Glucuronidase 9014-00-0, Luciferase 9031-11-2, .beta. Galactosidase 63774-46-9
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT 588746-25-2P
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(nucleotide sequence; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT 588746-26-3 588746-27-4 588746-28-5
RL: BSU (Biological study, unclassified); PRP (Properties); REM (Removal or disposal); BIOL (Biological study); PROC (Process)
(nucleotide sequence; attenuated Mycobacterium ***tuberculosis*** comprising deletion of RD1 region for vaccine prepns.)

IT 588747-89-1 588747-90-4 588747-91-5 588747-92-6 588747-93-7 588747-94-8 588747-95-9 588747-96-0
RL: PRP (Properties)
(unclaimed nucleotide sequence; attenuated Mycobacterium ***tuberculosis*** vaccines comprising deletion of RD1 region)

L11 ANSWER 3 OF 19 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN DUPLICATE 1

AN 2002:600487 BIOSIS <<LOGINID::20080330>>

DN PREV200200600487

TI Specialized transduction: An efficient method for generating marked and unmarked targeted gene disruptions in Mycobacterium ***tuberculosis*** , M. bovis BCG and M. smegmatis.

AU ***Bardarov, Stoyan*** ; Bardarov, Svetoslav; Pavelka, Martin S., Jr.; Sambandamurthy, Vasan; Larsen, Michelle; Tufariello, JoAnn; Chan, John; Hatfull, Graham; Jacobs, William R., Jr. [Reprint author]

CS Dept of Microbiology and Immunology, Howard Hughes Medical Institute, Albert Einstein College of Medicine, Bronx, NY, 10461, USA
jacobsw@hhmi.org

SO Microbiology (Reading), (October, 2002) Vol. 148, No. 10, pp. 3007-3017. print.
ISSN: 1350-0872.

DT Article

LA English

ED Entered STN: 20 Nov 2002
Last Updated on STN: 20 Nov 2002

AB The authors have developed a simple and highly efficient system for generating allelic exchanges in both fast- and slow-growing mycobacteria. In this procedure a gene of interest, disrupted by a selectable marker, is

cloned into a conditionally replicating (temperature-sensitive) shuttle phasmid to generate a specialized transducing mycobacteriophage. The temperature-sensitive mutations in the mycobacteriophage genome permit replication at the permissive temperature of 30degreeC but prevent replication at the non-permissive temperature of 37degreeC. Transduction at a non-permissive temperature results in highly efficient delivery of the recombination substrate to virtually all cells in the recipient population. The deletion mutations in the targeted genes are marked with antibiotic-resistance genes that are flanked by gammadelta-res (resolvase recognition target) sites. The transductants which have undergone a homologous recombination event can be conveniently selected on antibiotic-containing media. To demonstrate the utility of this genetic system seven different targeted gene disruptions were generated in three substrains of Mycobacterium bovis BCG, three strains of Mycobacterium ***tuberculosis*** , and Mycobacterium smegmatis. Mutants in the lysA, nadBC, panC, panCD, leuCD, Rv3291c and Rv0867c genes or operons were isolated as antibiotic-resistant (and in some cases auxotrophic) transductants. Using a plasmid encoding the gammadelta-resolvase (tnpR), the resistance genes could be removed, generating unmarked deletion mutations. It is concluded from the high frequency of allelic exchange events observed in this study that specialized transduction is a very efficient technique for genetic manipulation of mycobacteria and is a method of choice for constructing isogenic strains of M. ***tuberculosis*** , BCG or M. smegmatis which differ by defined mutations.

TI Specialized transduction: An efficient method for generating marked and unmarked targeted gene disruptions in Mycobacterium ***tuberculosis*** , M. bovis BCG and M. smegmatis.

AU ***Bardarov, Stoyan*** ; Bardarov, Svetoslav; Pavelka, Martin S., Jr.; Sambandamurthy, Vasan; Larsen, Michelle; Tufariello, JoAnn; Chan, John; Hatfull, Graham; Jacobs, William R.,. . .

AB. . . genetic system seven different targeted gene disruptions were generated in three substrains of Mycobacterium bovis BCG, three strains of Mycobacterium ***tuberculosis*** , and Mycobacterium smegmatis. Mutants in the lysA, nadBC, panC, panCD, leuCD, Rv3291c and Rv0867c genes or operons were isolated as. . . very efficient technique for genetic manipulation of mycobacteria and is a method of choice for constructing isogenic strains of M. ***tuberculosis*** , BCG or M. smegmatis which differ by defined mutations.

IT Major Concepts
Epidemiology (Population Studies); Infection; Molecular Genetics (Biochemistry and Molecular Biophysics); Pharmacology

IT Diseases
tuberculosis : bacterial disease
Tuberculosis (MeSH)

ORGN . . .
08881
Super Taxa
Mycobacteria; Actinomycetes and Related Organisms; Eubacteria; Bacteria; Microorganisms
Organism Name
Mycobacterium bovis BCG: pathogen
Mycobacterium bovis smegmatis: pathogen
Mycobacterium ***tuberculosis*** : pathogen
Taxa Notes
Bacteria, Eubacteria, Microorganisms

L11 ANSWER 4 OF 19 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
DUPLICATE 2
AN 2002:600482 BIOSIS <<LOGINID::20080330>>
DN PREV200200600482
TI Characterization of a Mycobacterium ***tuberculosis*** H37Rv transposon library reveals insertions in 351 ORFs and mutants with altered virulence.
AU McAdam, Ruth A.; Quan, Selwyn; Smith, Debbie A.; ***Bardarov, Stoyan*** ; Betts, Joanna C.; Cook, Fiona C.; Hooker, Elizabeth U.; Lewis, Alan P.; Woollard, Peter; Everett, Martin J.; Lukey, Pauline T.; Bancroft, Gregory J.; Jacobs, William R., Jr.; Duncan, Ken [Reprint author]
CS Medicines Research Centre, GlaxoSmithKline, Gunnels Wood Road, Stevenage, SG1 2NY, UK
kd9430@gsk.com
SO Microbiology (Reading), (October, 2002) Vol. 148, No. 10, pp. 2975-2986. print.
ISSN: 1350-0872.
DT Article
LA English
ED Entered STN: 20 Nov 2002
Last Updated on STN: 20 Nov 2002
AB A library of Mycobacterium ***tuberculosis*** insertional mutants was generated with the transposon Tn5370. The junction sequence between the transposon and the mycobacterial chromosome was determined, revealing the positions of 1329 unique insertions, 1189 of which were located in 351 different ORFs. Transposition was not completely random and examination of the most susceptible genome regions revealed a lower-than-average G+C content ranging from 54 to 62 mol%. Mutants were obtained in all of the recognized M. ***tuberculosis*** functional protein-coding gene classes. About 30% of the disrupted ORFs had matches elsewhere in the genome that suggested redundancy of function. The effect of gene disruption on the virulence of a selected set of defined mutants was investigated in a severe combined immune deficiency (SCID) mouse model. A range of phenotypes was observed in these mutants, the most notable being the severe attenuation in virulence of a strain disrupted in the Rv1290c gene, which encodes a protein of unknown function. The library described in this study provides a resource of defined mutant strains for use in functional analyses aimed at investigating the role of particular M. ***tuberculosis*** genes in virulence and defining their potential as targets for new anti-mycobacterial drugs or as candidates for deletion in a rationally attenuated live vaccine.
TI Characterization of a Mycobacterium ***tuberculosis*** H37Rv transposon library reveals insertions in 351 ORFs and mutants with altered virulence.
AU McAdam, Ruth A.; Quan, Selwyn; Smith, Debbie A.; ***Bardarov, Stoyan*** ; Betts, Joanna C.; Cook, Fiona C.; Hooker, Elizabeth U.; Lewis, Alan P.; Woollard, Peter; Everett, Martin J.; Lukey, Pauline. . .
AB A library of Mycobacterium ***tuberculosis*** insertional mutants was generated with the transposon Tn5370. The junction sequence between the transposon and the mycobacterial chromosome was determined,. . . revealed a lower-than-average G+C content ranging from 54 to 62 mol%. Mutants were obtained in all of the recognized M. ***tuberculosis*** functional protein-coding gene classes. About 30% of the disrupted ORFs had matches elsewhere in the genome that suggested redundancy of. . . provides a resource of defined mutant strains for use in functional analyses aimed at investigating the role of particular M. ***tuberculosis*** genes in virulence and defining their potential as

targets for new anti-mycobacterial drugs or as candidates for deletion in a. . .
IT Major Concepts
Infection; Molecular Genetics (Biochemistry and Molecular Biophysics)
IT Parts, Structures, & Systems of Organisms
chromosome
IT Diseases
tuberculosis : bacterial disease
Tuberculosis (MeSH)
IT Chemicals & Biochemicals
ORF [open reading frame]; Tn5370; proteins; transposon library
ORGN . . .
Mammals, Rodents, Vertebrates
ORGN Classifier
Mycobacteriaceae 08881
Super Taxa
Mycobacteria; Actinomycetes and Related Organisms; Eubacteria; Bacteria; Microorganisms
Organism Name
Mycobacterium ***tuberculosis*** : pathogen, strain-H37Rv
Taxa Notes
Bacteria, Eubacteria, Microorganisms

L11 ANSWER 5 OF 19 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
DUPLICATE 3
AN 2002:220802 BIOSIS <<LOGINID::20080330>>
DN PREV200200220802
TI Functional genomics reveals the sole sulphate transporter of the Mycobacterium ***tuberculosis*** complex and its relevance to the acquisition of sulphur in vivo.
AU Wooff, Esen; Michell, Stephen Li.; Gordon, Stephen V.; Chambers, Mark A.; ***Bardarov, Stoyan*** ; Jacobs, William R., Jr.; Hewinson, R. Glyn; Wheeler, Paul R. [Reprint author]
CS Tuberculosis Research Group, Veterinary Laboratories Agency-Weybridge, New Haw, Surrey, UK
pwheeler.via@gtnet.gov.uk
SO Molecular Microbiology, (February, 2002) Vol. 43, No. 3, pp. 653-663. print.
CODEN: MOMIEE. ISSN: 0950-382X.
DT Article
LA English
ED Entered STN: 3 Apr 2002
Last Updated on STN: 3 Apr 2002
AB Sulphur is essential for some of the most vital biological activities such as translation initiation and redox maintenance, and genes involved in sulphur metabolism have been implicated in virulence. Mycobacterium ***tuberculosis*** has three predicted genes for the prototrophic acquisition of sulphur as sulphate: cysA, part of an ABC transporter, and cysA2 and A3, SseC sulphotransferases. Screening for amino acid auxotrophs of Mycobacterium bovis BCG, obtained by transposon mutagenesis, was used to select methionine auxotrophs requiring a sulphur-containing amino acid for growth. We have characterized one of these auxotrophs as being disrupted in cysA. Both the cysA mutant and a previously identified mutant in an upstream gene, subl, were functionally characterized as being completely unable to take up sulphate. Complementation of the cysA mutant with the wild-type gene from M. ***tuberculosis*** restored prototrophy and the ability to take up sulphate with the functional

characteristics of an ABC transporter. Hence, it appears that this is the sole locus encoding inorganic sulphur transport in the M. ***tuberculosis*** complex.

TI Functional genomics reveals the sole sulphate transporter of the Mycobacterium ***tuberculosis*** complex and its relevance to the acquisition of sulphur in vivo.

AU Wooff, Esen; Michell, Stephen Li.; Gordon, Stephen V.; Chambers, Mark A.; ***Bardarov, Stoyan*** ; Jacobs, William R., Jr.; Hewinson, R. Glyn; Wheeler, Paul R. [Reprint author]

AB. . . activities such as translation initiation and redox maintenance, and genes involved in sulphur metabolism have been implicated in virulence. Mycobacterium ***tuberculosis*** has three predicted genes for the prototrophic acquisition of sulphur as sulphate: cysA, part of an ABC transporter, and cysA2. . . characterized as being completely unable to take up sulphate. Complementation of the cysA mutant with the wild-type gene from M. ***tuberculosis*** restored prototrophy and the ability to take up sulphate with the functional characteristics of an ABC transporter. Hence, it appears that this is the sole locus encoding inorganic sulphur transport in the M. ***tuberculosis*** complex.

ORGN . . .
08881
Super Taxa
Mycobacteria; Actinomycetes and Related Organisms; Eubacteria; Bacteria; Microorganisms
Organism Name
Mycobacterium bovis: strain-BCG, strain-EWP22, strain-EWP44, strain-EWc44, strain-sbpA
Mycobacterium ***tuberculosis***
Taxa Notes
Bacteria, Eubacteria, Microorganisms

GEN Mycobacterium ***tuberculosis*** cysA gene (Mycobacteriaceae); Mycobacterium ***tuberculosis*** cysA2 gene (Mycobacteriaceae); Mycobacterium ***tuberculosis*** cysA3 gene (Mycobacteriaceae)

L11 ANSWER 6 OF 19 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN

AN 2002:634261 BIOSIS <<LOGINID::20080330>>

DN PREV200200634261

TI The alternative sigma factor psi regulates major components of the oxidative and heat stress responses in Mycobacterium ***tuberculosis*** .

AU Raman, Sahadevan [Reprint author]; Song, Taeksun [Reprint author]; Puyang, Xiaoling [Reprint author]; Chen, Bing [Reprint author]; ***Bardarov,*** ***Stoyan*** [Reprint author]; Jacobs, William R., Jr.; Husson, Robert N. [Reprint author]

CS Division of Infectious Diseases, Children's Hospital, Harvard Medical School, Boston, MA, USA

SO Tuberculosis (Edinburgh), (2002) Vol. 82, No. 2-3, pp. 120. print.
Meeting Info.: 36th Annual Research Conference of the US-Japan Cooperative Medical Science Program Tuberculosis and Leprosy Panel. Louisiana, USA. July 15-17, 2001.
ISSN: 1472-9792.

DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)

LA English

ED Entered STN: 12 Dec 2002
Last Updated on STN: 12 Dec 2002

TI The alternative sigma factor psi regulates major components of the oxidative and heat stress responses in Mycobacterium ***tuberculosis***.
AU Raman, Sahadevan [Reprint author]; Song, Taeksun [Reprint author]; Puyang, Xiaoling [Reprint author]; Chen, Bing [Reprint author]; ***Bardarov,*** ***Stoyan*** [Reprint author]; Jacobs, William R., Jr.; Husson, Robert N. [Reprint author]
IT . . .
Bioenergetics (Biochemistry and Molecular Biophysics); Immune System (Chemical Coordination and Homeostasis); Infection; Molecular Genetics (Biochemistry and Molecular Biophysics)
IT Diseases
tuberculosis : bacterial disease, genetics, immunology
Tuberculosis (MeSH)
IT Chemicals & Biochemicals
SigH: alternative sigma factor; heat stress response components: regulation; oxidative stress response components: regulation
ORGN . . .
Rodents, Vertebrates
ORGN Classifier
Mycobacteriaceae 08881
Super Taxa
Mycobacteria; Actinomycetes and Related Organisms; Eubacteria; Bacteria; Microorganisms
Organism Name
Mycobacterium smegmatis
Mycobacterium ***tuberculosis*** : pathogen, strain-H37Rv
Taxa Notes
Bacteria, Eubacteria, Microorganisms
GEN Mycobacterium ***tuberculosis*** clpB gene (Mycobacteriaceae);
Mycobacterium ***tuberculosis*** dnaK gene (Mycobacteriaceae);
Mycobacterium ***tuberculosis*** sigB gene (Mycobacteriaceae);
Mycobacterium ***tuberculosis*** sigE gene (Mycobacteriaceae);
Mycobacterium ***tuberculosis*** thioredoxin reductase gene (Mycobacteriaceae)

L11 ANSWER 7 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN DUPLICATE 4
AN 2003:101202 CAPLUS <<LOGINID::20080330>>
DN 138:298304
TI Genetic methods for deciphering virulence determinants of Mycobacterium ***tuberculosis***
AU Braunstein, Miriam; ***Bardarov, Stoyan S.*** ; Jacobs, William R., Jr.
CS Department of Microbiology and Immunology, University of North Carolina, Chapel Hill, NC, 27599, USA
SO Methods in Enzymology (2002), 358(Bacterial Pathogenesis, Part C), 67-99
CODEN: MENZAU; ISSN: 0076-6879
PB Elsevier Science
DT Journal
LA English
AB The methods for directed allelic exchange and transposon mutagenesis that are used to engineer mutant strains of Mycobacterium ***tuberculosis*** are presented. Allelic exchange protocols based on plasmid transformation or a recently developed mycobacteriophage delivery system are also described, including the use of this delivery system for transposon mutagenesis of M. ***tuberculosis***. (c) 2002 Academic Press.
RE.CNT 79 THERE ARE 79 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Genetic methods for deciphering virulence determinants of Mycobacterium ***tuberculosis***

AU Braunstein, Miriam; ***Bardarov, Stoyan S.*** ; Jacobs, William R., Jr.

AB The methods for directed allelic exchange and transposon mutagenesis that are used to engineer mutant strains of Mycobacterium ***tuberculosis*** are presented. Allelic exchange protocols based on plasmid transformation or a recently developed mycobacteriophage delivery system are also described, including the use of this delivery system for transposon mutagenesis of M. ***tuberculosis*** . (c) 2002 Academic Press.

ST Mycobacterium ***tuberculosis*** virulence allelic exchange transposon mutagenesis

IT Genetic engineering
Mycobacterium ***tuberculosis***
Virulence (microbial)
(genetic methods for deciphering virulence determinants of Mycobacterium ***tuberculosis***)

IT ***Tuberculosis***
(methods for detg. pathogenesis of; genetic methods for deciphering virulence determinants of Mycobacterium ***tuberculosis***)

IT Gene
RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(methods for replacement of; genetic methods for deciphering virulence determinants of Mycobacterium ***tuberculosis***)

IT Molecular cloning
Transformation, genetic
(methods for; genetic methods for deciphering virulence determinants of Mycobacterium ***tuberculosis***)

IT Mutagenesis
(transposon; genetic methods for deciphering virulence determinants of Mycobacterium ***tuberculosis***)

L11 ANSWER 8 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2001:50775 CAPLUS <<LOGINID::20080330>>

DN 134:111213

TI One-step allelic exchange in Mycobacteria by forcing homologous recombination with a conditional transducing phage

IN Jacobs, William R., Jr.; ***Bardarov, Stoyan S.***

PA Albert Einstein College of Medicine of Yeshiva University, USA

SO PCT Int. Appl., 32 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001004267	A1	20010118	WO 2000-US40311	20000706
	WO 2001004267	A9	20020801		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PI US 6271034 B1 20010807 US 1999-350048 19990708
EP 1194526 A1 20020410 EP 2000-955918 20000706
EP 1194526 B1 20051026
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO
AT 307880 T 20051115 AT 2000-955918 20000706
PRAI US 1999-350048 A 19990708
WO 2000-US40311 W 20000706
AB The present invention provides a method for high frequency of allelic exchange in the slow-growing mycobacteria using in vitro generated specialized transducing mycobacteriophages, as well as the recombinant slow-growing mycobacteria generated using the disclosed method. A transducing mycobacteriophage of the present invention comprises a conditional mycobacteriophage contg. an E. coli bacteriophage lambda cosmid inserted into a non-essential region of the mycobacteriophage, said cosmid contg. a mutated DNA substrate which is homologous to a wildtype nucleic acid sequence of a slow-growing mycobacterium. When slow-growing mycobacteria infected with the conditional transducing phage are cultured under conditions wherein the conditional transducing phage does not replicate, e.g. at a non-permissive temp., the mutated DNA substrate is incorporated into the chromosomal DNA of the slow-growing mycobacteria by homologous recombination, thereby generating the recombinant slow-growing mycobacteria of the present invention. The disclosed method may be used to produce mycobacterial auxotrophs, including leucine and lysine auxotrophs. Use of the method to generate leucine auxotrophs by mutation of the leuCD genes and lysine auxotrophs by mutation of the lysA gene is demonstrated.
RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
IN Jacobs, William R., Jr.; ***Bardarov, Stoyan S.***
IT Mycobacterium BCG
Mycobacterium leprae
Mycobacterium ***tuberculosis***
(as slow-growing mycobacterium for allelic exchange; one-step allelic exchange in Mycobacteria by forcing homologous recombination with conditional transducing phage)

L11 ANSWER 9 OF 19 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
DUPLICATE 5
AN 2002:55083 BIOSIS <<LOGINID::20080330>>
DN PREV200200055083
TI Evidence that mycobacterial PEPGRS proteins are cell surface constituents that influence interactions with other cells.
AU Brennan, Michael J. [Reprint author]; Delogu, Giovanni; Chen, Yiping; ***Bardarov, Stoyan*** ; Kriakov, Jordan; Alavi, Mohammad; Jacobs, William R., Jr.
CS CBER/FDA, 29 Lincoln Dr. (HFM-431), Building 29, Room 502, Bethesda, MD, 20892, USA
Brennan@cber.fda.gov
SO Infection and Immunity, (December, 2001) Vol. 69, No. 12, pp. 7326-7333. print.
CODEN: INFIBR. ISSN: 0019-9567.
DT Article
LA English
ED Entered STN: 9 Jan 2002
Last Updated on STN: 25 Feb 2002
AB The elucidation of the genomic sequence of Mycobacterium

tuberculosis revealed the presence of a novel multigene family designated PE/PE-PGRS that encodes numerous, highly related proteins of unknown function. In this study, we demonstrate that a transposon insertion in a PE-PGRS gene (1818PE-PGRS) found in Mycobacterium bovis BCG Pasteur, which is the BCG homologue of the M. ***tuberculosis*** H37Rv gene Rv1818c, introduces new phenotypic properties to this BCG strain. These properties include dispersed growth in liquid medium and reduced infection of macrophages. Complementation of the 1818PE-PGRS::Tn5367 mutant with the wild-type gene restores both aggregative growth (clumping) in liquid medium and reestablishes infectivity of macrophages to levels equivalent to those for the parent BCG strain. Western blot analysis using antisera raised against the 1818PE-PGRS protein shows that PE-PGRS proteins are found in cell lysates of BCG and M. ***tuberculosis*** H37Ra and in the cell wall fraction of M. ***tuberculosis*** H37Rv. Moreover, immunofluorescent labeling of mycobacteria indicates that certain PE-PGRS proteins are localized at the cell surface of BCG and M. ***tuberculosis*** . Together these results suggest that certain PE-PGRS proteins may be found at the surface of mycobacteria and influence both cell surface interactions among mycobacteria as well as the interactions of mycobacteria with macrophages.

AU Brennan, Michael J. [Reprint author]; Delogu, Giovanni; Chen, Yiping; ***Bardarov, Stoyan*** ; Kriakov, Jordan; Alavi, Mohammad; Jacobs, William R., Jr.

AB The elucidation of the genomic sequence of Mycobacterium ***tuberculosis*** revealed the presence of a novel multigene family designated PE/PE-PGRS that encodes numerous, highly related proteins of unknown function. In. . . insertion in a PE-PGRS gene (1818PE-PGRS) found in Mycobacterium bovis BCG Pasteur, which is the BCG homologue of the M. ***tuberculosis*** H37Rv gene Rv1818c, introduces new phenotypic properties to this BCG strain. These properties include dispersed growth in liquid medium and. . . using antisera raised against the 1818PE-PGRS protein shows that PE-PGRS proteins are found in cell lysates of BCG and M. ***tuberculosis*** H37Ra and in the cell wall fraction of M. ***tuberculosis*** H37Rv. Moreover, immunofluorescent labeling of mycobacteria indicates that certain PE-PGRS proteins are localized at the cell surface of BCG and M. ***tuberculosis*** . Together these results suggest that certain PE-PGRS proteins may be found at the surface of mycobacteria and influence both cell. . .

ORGN Classifier
Mycobacteriaceae 08881
Super Taxa
Mycobacteria; Actinomycetes and Related Organisms; Eubacteria; Bacteria; Microorganisms
Organism Name
Mycobacterium bovis: genomic sequence, pathogen
Mycobacterium ***tuberculosis*** : genomic sequence, pathogen, strain-H37Ra, strain-H37Rv
Taxa Notes
Bacteria, Eubacteria, Microorganisms

GEN Mycobacterium ***tuberculosis*** Rv1818c gene (Mycobacteriaceae)

L11 ANSWER 10 OF 19 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN DUPLICATE 6

AN 2001:492816 BIOSIS <<LOGINID::20080330>>

DN PREV200100492816
TI The alternative sigma factor SigH regulates major components of oxidative and heat stress responses in Mycobacterium ***tuberculosis*** .
AU Raman, Sahadevan; Song, Taeksun; Puyang, Xiaoling; ***Bardarov,*** ***Stoyan*** ; Jacobs, William R., Jr.; Husson, Robert N. [Reprint author]
CS Children's Hospital, 300 Longwood Ave., Enders Rm. 609, Boston, MA, 02115, USA
robert.husson@tch.harvard.edu
SO Journal of Bacteriology, (October, 2001) Vol. 183, No. 20, pp. 6119-6125. print.
CODEN: JOBAAY. ISSN: 0021-9193.
DT Article
LA English
ED Entered STN: 24 Oct 2001
Last Updated on STN: 23 Feb 2002
AB Mycobacterium ***tuberculosis*** is a specialized intracellular pathogen that must regulate gene expression to overcome stresses produced by host defenses during infection. SigH is an alternative sigma factor that we have previously shown plays a role in the response to stress of the saprophyte Mycobacterium smegmatis. In this work we investigated the role of sigH in the M. ***tuberculosis*** response to heat and oxidative stress. We determined that a M. ***tuberculosis*** sigH mutant is more susceptible to oxidative stresses and that the inducible expression of the thioredoxin reductase/thioredoxin genes trxB2/trxC and a gene of unknown function, Rv2466c, is regulated by sigH via expression from promoters directly recognized by SigH. We also determined that the sigH mutant is more susceptible to heat stress and that inducible expression of the heat shock genes dnaK and clpB is positively regulated by sigH. The induction of these heat shock gene promoters but not of other SigH-dependent promoters was markedly greater in response to heat versus oxidative stress, consistent with their additional regulation by a heat-labile repressor. To further understand the role of sigH in the M. ***tuberculosis*** stress response, we investigated the regulation of the stress-responsive sigma factor genes sigE and sigB. We determined that inducible expression of sigE is regulated by sigH and that basal and inducible expression of sigB is dependent on sigE and sigH. These data indicate that sigH plays a central role in a network that regulates heat and oxidative-stress responses that are likely to be important in M. ***tuberculosis*** pathogenesis.
TI The alternative sigma factor SigH regulates major components of oxidative and heat stress responses in Mycobacterium ***tuberculosis*** .
AU Raman, Sahadevan; Song, Taeksun; Puyang, Xiaoling; ***Bardarov,*** ***Stoyan*** ; Jacobs, William R., Jr.; Husson, Robert N. [Reprint author]
AB Mycobacterium ***tuberculosis*** is a specialized intracellular pathogen that must regulate gene expression to overcome stresses produced by host defenses during infection. SigH. . . response to stress of the saprophyte Mycobacterium smegmatis. In this work we investigated the role of sigH in the M. ***tuberculosis*** response to heat and oxidative stress. We determined that a M. ***tuberculosis*** sigH mutant is more susceptible to oxidative stresses and that the inducible expression of the thioredoxin reductase/thioredoxin genes trxB2/trxC and. . . stress, consistent with their additional regulation by a heat-labile repressor. To further understand the role of sigH in the M. ***tuberculosis*** stress response, we investigated the regulation of the stress-responsive sigma factor genes sigE and sigB. We determined

that inducible expression. . . a central role in a network that regulates heat and oxidative-stress responses that are likely to be important in M. ***tuberculosis*** pathogenesis.

ORGN Classifier
Mycobacteriaceae 08881
Super Taxa
Mycobacteria; Actinomycetes and Related Organisms; Eubacteria; Bacteria; Microorganisms
Organism Name
Mycobacterium ***tuberculosis*** : pathogen, strain-H37Rv
Taxa Notes
Bacteria, Eubacteria, Microorganisms

GEN Mycobacterium ***tuberculosis*** Rv2466c gene (Mycobacteriaceae); Mycobacterium ***tuberculosis*** SigH gene (Mycobacteriaceae); Mycobacterium ***tuberculosis*** clpB gene (Mycobacteriaceae): expression; Mycobacterium ***tuberculosis*** dnaK gene (Mycobacteriaceae): expression; Mycobacterium ***tuberculosis*** sigE gene (Mycobacteriaceae): expression; Mycobacterium ***tuberculosis*** trxB2 gene (Mycobacteriaceae): expression; Mycobacterium ***tuberculosis*** trxC gene (Mycobacteriaceae): expression

L11 ANSWER 11 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2001:475989 CAPLUS <<LOGINID::20080330>>
DN 136:80510
TI Transposon mutagenesis in mycobacteria using conditionally replicating mycobacteriophages
AU ***Bardarov, Stoyan S.*** ; Bardarov, Svetoslav S., Jr.; Jacobs, William R., Jr.
CS Howard Hughes Medical Institute, Department of Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, NY, USA
SO Methods in Molecular Medicine (2001), 54(Mycobacterium tuberculosis Protocols), 43-57
CODEN: MMMEFN
PB Humana Press Inc.
DT Journal
LA English
AB A detailed protocol for the generation of Tn5367 transposon libraries in Mycobacterium bovis BCG and Mycobacterium ***tuberculosis*** using the conditionally replicating mycobacteriophage phAE94 as delivery vector is described. The structure and classification of the mobile genetic elements as well as transposable elements in mycobacteria is also discussed.
RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AU ***Bardarov, Stoyan S.*** ; Bardarov, Svetoslav S., Jr.; Jacobs, William R., Jr.
AB A detailed protocol for the generation of Tn5367 transposon libraries in Mycobacterium bovis BCG and Mycobacterium ***tuberculosis*** using the conditionally replicating mycobacteriophage phAE94 as delivery vector is described. The structure and classification of the mobile genetic elements. . .
IT Mycobacterium
Mycobacterium BCG
Mycobacterium ***tuberculosis***
(transposon mutagenesis in mycobacteria using conditionally replicating mycobacteriophages)

L11 ANSWER 12 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2001:677696 CAPLUS <<LOGINID::20080330>>
DN 136:397957
TI Advanced development of the digital ***tuberculosis*** tester for MDR-TB screening
AU Smith, Jason E.; Simkulet, Michelle D.; Gutin, Alexander; Gutin, Alexy; ***Bardarov, Savco*** ; Jacobs, William R., Jr.; Castracane, James; Tang, Oliver; Riska, Paul
CS InterScience, Inc., Troy, NY, USA
SO Proceedings of SPIE-The International Society for Optical Engineering (2001), 4255(Clinical Diagnostic Systems), 9-15
CODEN: PSISDG; ISSN: 0277-786X
PB SPIE-The International Society for Optical Engineering
DT Journal
LA English
AB ***Tuberculosis*** (TB) remains the leading cause of death in the world from a single infectious disease, and the threat is becoming more crit. with the spread of multi-drug resistant ***Tuberculosis*** (MDR-TB). TB detection, and susceptibility testing for drug resistant strain identification, is advancing with the development of Luciferase Reporter Mycobacteriophages (LRM). LRM will emit visible light at very low intensity when in the presence of live mycobacteria cells such as ***Tuberculosis*** strains. InterScience, Inc., together with its collaboration, is developing a highly sensitive, real-time digital detection system for the anal. of luminescent assays. Recent advances in system sensitivity, design, and implementation, as well as preliminary results of the development of individual test cartridges, will be presented. The ultimate goal of this work is to provide a versatile luminescence detection tool for widespread research and clin. applications.
RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
TI Advanced development of the digital ***tuberculosis*** tester for MDR-TB screening
AU Smith, Jason E.; Simkulet, Michelle D.; Gutin, Alexander; Gutin, Alexy; ***Bardarov, Savco*** ; Jacobs, William R., Jr.; Castracane, James; Tang, Oliver; Riska, Paul
AB ***Tuberculosis*** (TB) remains the leading cause of death in the world from a single infectious disease, and the threat is becoming more crit. with the spread of multi-drug resistant ***Tuberculosis*** (MDR-TB). TB detection, and susceptibility testing for drug resistant strain identification, is advancing with the development of Luciferase Reporter Mycobacteriophages. . . (LRM). LRM will emit visible light at very low intensity when in the presence of live mycobacteria cells such as ***Tuberculosis*** strains. InterScience, Inc., together with its collaboration, is developing a highly sensitive, real-time digital detection system for the anal. of. . .
ST advanced development digital ***tuberculosis*** tester MDR TB screening
IT Charge coupled devices
Clinical analyzers
Imaging
Luminescence spectroscopy
Multidrug resistance
(advanced development of digital ***tuberculosis*** tester for

MDR-TB screening)
IT Containers
(cartridges; advanced development of digital ***tuberculosis*** tester for MDR-TB screening)
IT Bacteriophage
(luciferase reporter mycobacteriophages; advanced development of digital ***tuberculosis*** tester for MDR-TB screening)
IT Mycobacterium ***tuberculosis***
Tuberculosis
(multi-drug resistant; advanced development of digital ***tuberculosis*** tester for MDR-TB screening)
IT Drug screening
(susceptibility testing; advanced development of digital ***tuberculosis*** tester for MDR-TB screening)
IT 9014-00-0, Luciferase
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(advanced development of digital ***tuberculosis*** tester for MDR-TB screening)

L11 ANSWER 13 OF 19 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN DUPLICATE 7
AN 2000:222891 BIOSIS <<LOGINID::20080330>>
DN PREV200000222891
TI Attenuation of and protection induced by a leucine auxotroph of Myobacterium ***tuberculosis*** .
AU Hondalus, Mary K.; ***Bardarov, Stoyan*** ; Russell, Robert; Chan, John; Jacobs, William R., Jr.; Bloom, Barry R. [Reprint author]
CS School of Public Health, Harvard University, 665 Huntington Ave., Boston, MA, 02115, USA
SO Infection and Immunity, (May, 2000) Vol. 68, No. 5, pp. 2888-2898. print. CODEN: INFIBR. ISSN: 0019-9567.
DT Article
LA English
ED Entered STN: 31 May 2000
Last Updated on STN: 5 Jan 2002
AB Attenuated mutants of Mycobacterium ***tuberculosis*** represent potential vaccine candidates for the prevention of ***tuberculosis*** . It is known that auxotrophs of a variety of bacteria are attenuated in vivo and yet provide protection against challenge with wild-type organisms. A leucine auxotroph of M. ***tuberculosis*** was created by allelic exchange, replacing wild-type leuD (Rv2987c), encoding isopropyl malate isomerase, with a mutant copy of the gene in which 359 bp had been deleted, creating a strain requiring exogenous leucine supplementation for growth in vitro. The frequency of reversion to prototrophy was <10-11. In contrast to wild-type M. ***tuberculosis*** , the DELTAleuD mutant was unable to replicate in macrophages in vitro. Its attenuation in vivo and safety as a vaccine were established by the fact that it caused no deaths in immunodeficient SCID mice. Complementation of the mutant with wild-type leuD abolished the requirement for leucine supplementation and restored the ability of the strain to grow both in macrophages and in SCID mice, thus confirming that the attenuated phenotype was due to the DELTAleuD mutation. As a test of the vaccine potential of the leucine auxotroph, immunocompetent BALB/c mice, susceptible to fatal infection with wild-type M. ***tuberculosis*** , were immunized with the DELTAleuD mutant and subsequently challenged with virulent M. ***tuberculosis*** by both the intravenous and aerosol routes. A comparison group of mice was

immunized with conventional Mycobacterium bovis BCG vaccine. Whereas all unvaccinated mice succumbed to intravenous infection within 15 weeks, mice immunized with either BCG or the DELTAleuD mutant of M.
tuberculosis exhibited enhanced and statistically equivalent survival curves. However, the leuD auxotroph was less effective than live BCG in reducing organ burdens and tissue pathology of mice challenged by either route. We conclude that attenuation and protection against M.
tuberculosis challenge can be achieved with a leucine auxotroph and suggest that to induce optimal protection, attenuated strains of M.
tuberculosis should persist long enough and be sufficiently metabolically active to synthesize relevant antigens for an extended period of time.

TI Attenuation of and protection induced by a leucine auxotroph of Myobacterium ***tuberculosis*** .

AU Hondalus, Mary K.; ***Bardarov, Stoyan*** ; Russell, Robert; Chan, John; Jacobs, William R., Jr.; Bloom, Barry R. [Reprint author]

AB Attenuated mutants of Mycobacterium ***tuberculosis*** represent potential vaccine candidates for the prevention of ***tuberculosis*** . It is known that auxotrophs of a variety of bacteria are attenuated in vivo and yet provide protection against challenge with wild-type organisms. A leucine auxotroph of M. ***tuberculosis*** was created by allelic exchange, replacing wild-type leuD (Rv2987c), encoding isopropyl malate isomerase, with a mutant copy of the gene. . . exogenous leucine supplementation for growth in vitro. The frequency of reversion to prototrophy was <10-11. In contrast to wild-type M.
tuberculosis , the DELTAleuD mutant was unable to replicate in macrophages in vitro. Its attenuation in vivo and safety as a vaccine. . . a test of the vaccine potential of the leucine auxotroph, immunocompetent BALB/c mice, susceptible to fatal infection with wild-type M. ***tuberculosis*** , were immunized with the DELTAleuD mutant and subsequently challenged with virulent M. ***tuberculosis*** by both the intravenous and aerosol routes. A comparison group of mice was immunized with conventional Mycobacterium bovis BCG vaccine.. . . unvaccinated mice succumbed to intravenous infection within 15 weeks, mice immunized with either BCG or the DELTAleuD mutant of M.
tuberculosis exhibited enhanced and statistically equivalent survival curves. However, the leuD auxotroph was less effective than live BCG in reducing organ burdens and tissue pathology of mice challenged by either route. We conclude that attenuation and protection against M.
tuberculosis challenge can be achieved with a leucine auxotroph and suggest that to induce optimal protection, attenuated strains of M.
tuberculosis should persist long enough and be sufficiently metabolically active to synthesize relevant antigens for an extended period of time.

IT . . .
(Chemical Coordination and Homeostasis); Pharmacology

IT Parts, Structures, & Systems of Organisms
macrophage: blood and lymphatics, immune system

IT Diseases
tuberculosis : bacterial disease
Tuberculosis (MeSH)

IT Chemicals & Biochemicals
Mycobacterium ***tuberculosis*** leuD gene

ORGN . . .
Mammals, Rodents, Vertebrates

ORGN Classifier
Mycobacteriaceae 08881

Super Taxa
Mycobacteria; Actinomycetes and Related Organisms; Eubacteria; Bacteria; Microorganisms
Organism Name
Mycobacterium ***tuberculosis*** : candidate vaccine, pathogen
Taxa Notes
Bacteria, Eubacteria, Microorganisms

L11 ANSWER 14 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2000:516172 CAPLUS <<LOGINID::20080330>>
DN 134:127938
TI Development of an advanced digital detection system for multidrug resistant ***tuberculosis*** screening
AU Simkulet, Michelle D.; Beckstead, Jeffrey A.; Gilman, Brian C.; ***Bardarov, Savco*** ; Castracane, James; Jacobs, William R., Jr.
CS InterScience, Inc., Troy, NY, USA
SO Proceedings of SPIE-The International Society for Optical Engineering (2000), 3924(Molecular Imaging: Reporters, Dyes, Markers, and Instrumentation), 48-54
CODEN: PSISDG; ISSN: 0277-786X
PB SPIE-The International Society for Optical Engineering
DT Journal
LA English
AB ***Tuberculosis*** (TB) remains the leading cause of death in the world from a single infectious disease and the threat is becoming more crit. with the emergence and spread of multi-drug resistant ***tuberculosis*** (MDR-TB). Existing methods for detection of various strains of Mycobacterium ***tuberculosis*** are complex, time consuming and expensive, and therefore, not suitable for use in developing countries where the spread of the disease is most rampant. Currently, a digital detection system based on advanced digital imaging technol., including CMOS and image intensification technol., is being developed by InterScience, Inc. For use with the luciferase reporter mycobacteriophages technique as developed at the Albert Einstein College of Medicine. This compact, low cost and high sensitivity system for rapid diagnosis and drug susceptibility testing for TB will have an immediate impact for both research and clin. applications. It is envisioned that the instrument will be suitable for use as a portable tool for rapid screening of MDR-TB in both developed and developing countries. The development of the system, recent results and a comparison to competing technologies will be presented.
RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
TI Development of an advanced digital detection system for multidrug resistant ***tuberculosis*** screening
AU Simkulet, Michelle D.; Beckstead, Jeffrey A.; Gilman, Brian C.; ***Bardarov, Savco*** ; Castracane, James; Jacobs, William R., Jr.
AB ***Tuberculosis*** (TB) remains the leading cause of death in the world from a single infectious disease and the threat is becoming more crit. with the emergence and spread of multi-drug resistant ***tuberculosis*** (MDR-TB). Existing methods for detection of various strains of Mycobacterium ***tuberculosis*** are complex, time consuming and expensive, and therefore, not suitable for use in developing countries where the spread of the. . .
ST advanced digital detection system multidrug ***tuberculosis*** screening
IT Clinical analyzers

(Advanced digital detection system; development of advanced digital detection system for multidrug resistant ***tuberculosis*** screening)

IT Antibiotics
Diagnosis
Multidrug resistance
Mycobacterium ***tuberculosis***
Tuberculosis
(development of advanced digital detection system for multidrug resistant ***tuberculosis*** screening)

IT Imaging
(digital; development of advanced digital detection system for multidrug resistant ***tuberculosis*** screening)

IT 9014-00-0, Luciferase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(development of advanced digital detection system for multidrug resistant ***tuberculosis*** screening)

L11 ANSWER 15 OF 19 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN

AN 2000:278900 BIOSIS <<LOGINID::20080330>>

DN PREV200000278900

TI TM4 conditional shuttle phasmids and uses thereof.

AU Jacobs, William R. [Inventor, Reprint author]; ***Bardarov, Stoyan*** [Inventor]; Hatfull, Graham F. [Inventor]

CS Pittsburgh, PA, USA
ASSIGNEE: Albert Einstein College of Medicine of Yeshiva University, Bronx, NY, USA; University of Pittsburgh, Pittsburgh, PA, USA

PI US 5972700 19991026

SO Official Gazette of the United States Patent and Trademark Office Patents, (Oct. 26, 1999) Vol. 1227, No. 4. e-file.
CODEN: OGUPE7. ISSN: 0098-1133.

DT Patent

LA English

ED Entered STN: 6 Jul 2000
Last Updated on STN: 7 Jan 2002

AB The present invention provides a conditional shuttle phasmid constructed by inserting a cosmid into a non-essential region of the TM4 mycobacteriophage that introduces DNA of interest into mycobacteria, especially M. ***tuberculosis*** complex organisms and other slow growing mycobacteria. The present invention provides a recombinant mycobacterium which expresses a DNA of interest incorporated into its chromosome by a TM4 conditional shuttle phasmid containing the DNA of interest. The present invention further provides a mycobacterial auxotrophic mutant and a method of generating auxotrophic mutants.

AU Jacobs, William R. [Inventor, Reprint author]; ***Bardarov, Stoyan*** [Inventor]; Hatfull, Graham F. [Inventor]

AB. . . inserting a cosmid into a non-essential region of the TM4 mycobacteriophage that introduces DNA of interest into mycobacteria, especially M. ***tuberculosis*** complex organisms and other slow growing mycobacteria. The present invention provides a recombinant mycobacterium which expresses a DNA of interest. . .

L11 ANSWER 16 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN

AN 1999:233991 CAPLUS <<LOGINID::20080330>>

DN 130:263163

TI Shuttle phasmids for mycobacteria with a conditional replicon based upon

mycobacteriophage TM4
IN Jacobs, William R., Jr.; ***Bardarov, Stoyan*** ; Hatfull, Graham F.
PA Albert Einstein College of Medicine of Yeshiva University, USA
SO PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9916868	A1	19990408	WO 1998-US19766	19980922
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 5972700	A	19991026	US 1997-938059	19970926
	AU 9894029	A	19990423	AU 1998-94029	19980922
	EP 1017796	A1	20000712	EP 1998-947197	19980922
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	ZA 9808719	A	19990413	ZA 1998-8719	19980923
PRAI	US 1997-938059	A	19970926		
	WO 1998-US19766	W	19980922		

AB A shuttle phasmid that can be used to investigate the genetics of mycobacteria, esp. the Mycobacterium ***tuberculosis*** complex, is described. The phasmid is constructed by inserting a cosmid into a non-essential region of the TM4 mycobacteriophage and because the replication of the phasmid is conditional it can be used to introduce transposons that will transpose under non-permissive conditions and act as mutagens. Auxotrophic mutants can therefore be generated. A no. of other manipulations, such as transient or stable expression of foreign genes, gene deletion and inactivation can be brought about using these vectors. Phasmids with a temp.-sensitive replicon, capable of replication at 30.degree. but not at 42.degree. were screened for by inhibition of plaque growth at 42.degree. after initial plaque formation at 37.degree.. Transposition of Tn5367 in a no. of species of Mycobacterium after introduction with one of these phasmids is demonstrated. The transposition showed no sequence specificity for the site of insertion in M. ***tuberculosis*** of Mycobacterium BCG. A no. of mutations are characterized.
RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
IN Jacobs, William R., Jr.; ***Bardarov, Stoyan*** ; Hatfull, Graham F.
AB A shuttle phasmid that can be used to investigate the genetics of mycobacteria, esp. the Mycobacterium ***tuberculosis*** complex, is described. The phasmid is constructed by inserting a cosmid into a non-essential region of the TM4 mycobacteriophage and. . . with one of these phasmids is demonstrated. The transposition showed no sequence specificity for the site of insertion in M. ***tuberculosis*** of Mycobacterium BCG. A no. of mutations are characterized.
IT Elongation factors (protein formation)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(EF-G, transposon mutagenesis of Mycobacterium ***tuberculosis***

gene for; shuttle phasmids for mycobacteria with conditional replicon based upon mycobacteriophage TM4)

IT Ferritins
RL: BSU (Biological study, unclassified); BIOL (Biological study) (H (heart-type), transposon mutagenesis of Mycobacterium ***tuberculosis*** gene for; shuttle phasmids for mycobacteria with conditional replicon based upon mycobacteriophage TM4)

IT Gene, microbial
RL: BSU (Biological study, unclassified); BIOL (Biological study) (bioF, transposon mutagenesis in Mycobacterium ***tuberculosis*** of; shuttle phasmids for mycobacteria with conditional replicon based upon mycobacteriophage TM4)

IT Gene, microbial
RL: BSU (Biological study, unclassified); BIOL (Biological study) (efg, transposon mutagenesis in Mycobacterium ***tuberculosis*** of; shuttle phasmids for mycobacteria with conditional replicon based upon mycobacteriophage TM4)

IT Gene, microbial
RL: BSU (Biological study, unclassified); BIOL (Biological study) (leuD, transposon mutagenesis in Mycobacterium ***tuberculosis*** of; shuttle phasmids for mycobacteria with conditional replicon based upon mycobacteriophage TM4)

IT Gene, microbial
RL: BSU (Biological study, unclassified); BIOL (Biological study) (rsgA, transposon mutagenesis in Mycobacterium ***tuberculosis*** of; shuttle phasmids for mycobacteria with conditional replicon based upon mycobacteriophage TM4)

IT Mycobacterium
Mycobacterium BCG
Mycobacterium bovis
Mycobacterium phage TM4
Mycobacterium phlei
Mycobacterium smegmatis
Mycobacterium ***tuberculosis***
(shuttle phasmids for mycobacteria with conditional replicon based upon mycobacteriophage TM4)

IT 9012-31-1, Acetyl-CoA synthase 9014-48-6, Transketolase 9024-35-5, IGP dehydratase 9026-04-4, Thiosulfate sulfur transferase 9031-72-5, Alcohol dehydrogenase 79956-01-7, Polyketide synthase
RL: BSU (Biological study, unclassified); BIOL (Biological study) (transposon mutagenesis of Mycobacterium ***tuberculosis*** gene for; shuttle phasmids for mycobacteria with conditional replicon based upon mycobacteriophage TM4)

L11 ANSWER 17 OF 19 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN DUPLICATE 8

AN 1997:488738 BIOSIS <<LOGINID::20080330>>

DN PREV199799787941

TI Conditionally replicating mycobacteriophages: A system for transposon delivery to Mycobacterium ***tuberculosis*** .

AU ***Bardarov, Stoyan*** ; Kriakov, Jordan; Carriere, Christian; Yu, Shengwei; Vaamonde, Carlos; McAdam, Ruth A.; Bloom, Barry R.; Hatfull, Graham F.; Jacobs, William R., Jr. [Reprint author]

CS Howard Hughes Med. Inst., Dep. Microbiol. Immunol., Albert Einstein College Med., 1300 Morris Park Ave., Bronx, NY 10461, USA

SO Proceedings of the National Academy of Sciences of the United States of America, (1997) Vol. 94, No. 20, pp. 10961-10966.

CODEN: PNASA6. ISSN: 0027-8424.
DT Article
LA English
ED Entered STN: 7 Nov 1997
Last Updated on STN: 7 Nov 1997
AB Transposon mutagenesis provides a direct selection for mutants and is an extremely powerful technique to analyze genetic functions in a variety of prokaryotes. Transposon mutagenesis of Mycobacterium ***tuberculosis*** has been limited in part because of the inefficiency of the delivery systems. This report describes the development of conditionally replicating shuttle plasmids from the mycobacteriophages D29 and TM4 that enable efficient delivery of transposons into both fast- and slow-growing mycobacteria. These shuttle plasmids consist of an Escherichia coli cosmid vector containing either a mini-Tn10(kan) or Tn5367 inserted into a nonessential region of the phage genome. Thermosensitive mutations were created in the mycobacteriophage genome that allow replication at 30 degree C but not at 37 degree C (TM4) or 38.5 degree C (D29). Infection of mycobacteria at the nonpermissive temperature results in highly efficient transposon delivery to the entire population of mycobacterial cells. Transposition of mini-Tn10(kan) occurred in a site-specific fashion in M. smegmatis whereas Tn5367 transposed apparently randomly in M. phlei, Bacille Calmette-Guerin (BCG), and M. ***tuberculosis*** . Sequence analysis of the M. ***tuberculosis*** and BCG chromosomal regions adjacent to Tn5367 insertions, in combination with M. ***tuberculosis*** genomic sequence and physical map data, indicates that the transpositions have occurred randomly in diverse genes in every quadrant of the genome. Using this system, it has been readily possible to generate libraries containing thousands of independent mutants of M. phlei, BCG, and M. ***tuberculosis*** .
TI Conditionally replicating mycobacteriophages: A system for transposon delivery to Mycobacterium ***tuberculosis*** .
AU ***Bardarov, Stoyan*** ; Kriakov, Jordan; Carriere, Christian; Yu, Shengwei; Vaamonde, Carlos; McAdam, Ruth A.; Bloom, Barry R.; Hatfull, Graham F.; Jacobs, William. . .
AB. . . mutants and is an extremely powerful technique to analyze genetic functions in a variety of prokaryotes. Transposon mutagenesis of Mycobacterium ***tuberculosis*** has been limited in part because of the inefficiency of the delivery systems. This report describes the development of conditionally. . . in a site-specific fashion in M. smegmatis whereas Tn5367 transposed apparently randomly in M. phlei, Bacille Calmette-Guerin (BCG), and M. ***tuberculosis*** . Sequence analysis of the M. ***tuberculosis*** and BCG chromosomal regions adjacent to Tn5367 insertions, in combination with M. ***tuberculosis*** genomic sequence and physical map data, indicates that the transpositions have occurred randomly in diverse genes in every quadrant of. . . system, it has been readily possible to generate libraries containing thousands of independent mutants of M. phlei, BCG, and M. ***tuberculosis*** .
ORGN Classifier
Mycobacteriaceae 08881
Super Taxa
Mycobacteria; Actinomycetes and Related Organisms; Eubacteria; Bacteria; Microorganisms
Organism Name
Mycobacterium ***tuberculosis***
Taxa Notes
Bacteria, Eubacteria, Microorganisms

ORGN Classifier
Viruses 03000
Super Taxa
Microorganisms
Organism Name
bacterial viruses
Taxa Notes
Microorganisms, Viruses

L11 ANSWER 18 OF 19 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN DUPLICATE 9
AN 1998:34852 BIOSIS <<LOGINID::20080330>>
DN PREV199800034852
TI Conditionally replicating Luciferase Reporter Phages: Improved sensitivity for rapid detection and assessment of drug susceptibility of Mycobacterium ***tuberculosis*** .
AU Carriere, Christian; Riska, Paul F.; Zimhony, Oren; Kriakov, Jordan; ***Bardarov, Stoyan*** ; Burns, Judah; Chan, John; Jacobs, William R., Jr. [Reprint author]
CS Howard Hughes Med. Inst., Albert Einstein Coll. Med. Yeshiva Univ., 1300 Morris Park Ave., Bronx, NY 10461, USA
SO Journal of Clinical Microbiology, (Dec., 1997) Vol. 35, No. 12, pp. 3232-3239. print.
CODEN: JCMIDW. ISSN: 0095-1137.
DT Article
LA English
ED Entered STN: 14 Jan 1998
Last Updated on STN: 14 Jan 1998
AB TM4 is a lytic mycobacteriophage which infects mycobacteria of clinical importance. A luciferase reporter phage, phAE40, has been constructed from TM4 and was previously shown to be useful for the rapid detection and drug susceptibility testing of Mycobacterium ***tuberculosis*** . However, the lytic nature of the phage results in a loss of detectable light output and limits the sensitivity of detection. We describe several strategies aimed at improving the luciferase activity generated by TM4 luciferase phages, including (i) varying the position of the luciferase gene in the phage genome, (ii) isolating host-range mutants of the phage, and (iii) introducing temperature-sensitive mutations in the phage such that it will not replicate at the infecting temperature. Several new phages generated by these methods show increased intensity of luciferase production compared to the first-generation reporter phage phAE40, and one phage, phAE88, also demonstrates an enhanced duration of luciferase activity. This has allowed the detection of as few as 120 BCG cells and the determination of drug susceptibilities of M. ***tuberculosis*** in as little as 1 day.
TI Conditionally replicating Luciferase Reporter Phages: Improved sensitivity for rapid detection and assessment of drug susceptibility of Mycobacterium ***tuberculosis*** .
AU Carriere, Christian; Riska, Paul F.; Zimhony, Oren; Kriakov, Jordan; ***Bardarov, Stoyan*** ; Burns, Judah; Chan, John; Jacobs, William R., Jr. [Reprint author]
AB. . . constructed from TM4 and was previously shown to be useful for the rapid detection and drug susceptibility testing of Mycobacterium ***tuberculosis*** . However, the lytic nature of the phage results in a
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of drug susceptibilities of M. ***tuberculosis*** in as little as 1 day.
ORGN . . .
Mycobacteriaceae 08881
Super Taxa
Mycobacteria; Actinomycetes and Related Organisms; Eubacteria; Bacteria; Microorganisms
Organism Name
Mycobacterium-bovis: drug susceptibility, host
Mycobacterium-smegmatis: drug susceptibility, host
Mycobacterium- ***tuberculosis*** : drug susceptibility, host
Taxa Notes
Bacteria, Eubacteria, Microorganisms
ORGN Classifier
Viruses 03000
Super Taxa
Microorganisms
Organism Name
phAE40: conditional replication,. . .

L11 ANSWER 19 OF 19 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN DUPLICATE 10
AN 1996:75893 BIOSIS <<LOGINID::20080330>>
DN PREV199698648028
TI Allelic exchange in Mycobacterium ***tuberculosis*** with long linear recombination substrates.
AU Balasubramanian, V.; Pavelka., Martin S., Jr.; ***Bardarov, Stoyan S.*** ; Maratin, Jean; Weisbrod, Torin R.; McAdam, Ruth A.; Bloom, Barry R.; Jacobs, William R., Jr. [Reprint author]
CS Dep. Microbiol. Immunol., Albert Einstein Coll. Med., 1300 Morris Park Ave., Bronx, NY 10461, USA
SO Journal of Bacteriology, (1996) Vol. 178, No. 1, pp. 273-279.
CODEN: JOBAAY. ISSN: 0021-9193.
DT Article
LA English
ED Entered STN: 27 Feb 1996
Last Updated on STN: 28 Feb 1996
AB Genetic studies of Mycobacterium ***tuberculosis*** have been greatly hampered by the inability to introduce specific chromosomal mutations. Whereas the ability to perform allelic exchanges has provided a useful method of gene disruption in other organisms, in the clinically important species of mycobacteria, such as M. ***tuberculosis*** and Mycobacterium bovis, similar approaches have thus far been unsuccessful. In this communication, we report the development of a shuttle mutagenesis strategy that involves the use of long linear recombination substrates to reproducibly obtain recombinants by allelic exchange in M. ***tuberculosis*** . Long linear recombination substrates, approximately 40 to 50 kb in length, were generated by constructing libraries in the excisable cosmid vector pYUB328. The cosmid vector could be readily excised from the recombinant cosmids by digestion with PacI, a restriction endonuclease for which there exist few, if any, sites in mycobacterial genomes. A cosmid containing the mycobacterial leuD gene was isolated, and a selectable marker conferring resistance to kanamycin was inserted into the leuD gene in the recombinant cosmid by interplasmid recombination in Escherichia coli. A long linear recombination substrate containing the insertionally mutated leuD gene was generated by PacI digestion.

Electroporation of this recombination substrate containing the insertionally mutated leuD allele resulted in the generation of leucine auxotrophic mutants by homologous recombination in 6% of the kanamycin-resistant transformants for both the Erdman and H37Rv strains of M. ***tuberculosis*** . The ability to perform allelic exchanges provides an important approach for investigating the biology of this pathogen as well as developing new live-cell M. ***tuberculosis*** -based vaccines.

TI Allelic exchange in Mycobacterium ***tuberculosis*** with long linear recombination substrates.

AU Balasubramanian, V.; Pavelka., Martin S., Jr.; ***Bardarov, Stoyan S.*** ; Maratin, Jean; Weisbrod, Torin R.; McAdam, Ruth A.; Bloom, Barry R.; Jacobs, William R., Jr. [Reprint author]

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ORGN . . .
Eubacteria, Microorganisms

ORGN Classifier
Mycobacteriaceae 08881

Super Taxa
Mycobacteria; Actinomycetes and Related Organisms; Eubacteria; Bacteria; Microorganisms

Organism Name
Mycobacterium bovis
Mycobacterium ***tuberculosis***

Taxa Notes
Bacteria, Eubacteria, Microorganisms